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Neuroinflammation and Blood-Brain Barrier Disruption Following Traumatic Brain Injury: Pathophysiology and Potential Therapeutic Targets

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Abstract

Traumatic Brain Injury (TBI) is the most frequent cause of death and disability in young adults and children in the developed world, occurring in over 1.7 million persons and resulting in 50,000 deaths in the United States alone. The Centers for Disease Control and Prevention estimate that between 3.2 and 5.3 million persons in the United States live with a TBI-related disability, including several neurocognitive disorders and functional limitations. Following the primary mechanical injury in TBI, literature suggests the presence of a delayed secondary injury involving a variety of neuroinflammatory changes. In the hours to days following a TBI, several signaling molecules and metabolic derangements result in disruption of the blood-brain barrier (BBB), leading to an extravasation of immune cells and cerebral edema. The primary, sudden injury in TBI occurs as a direct result of impact and therefore cannot be treated, but the timeline and pathophysiology of the delayed, secondary injury allows for a window of possible therapeutic options. The goal of this review is to discuss the pathophysiology of the primary and delayed injury in TBI as well as present several preclinical studies that identify molecular targets in the potential treatment of TBI. Additionally, certain recent clinical trials are briefly discussed to demonstrate the current state of TBI investigation.

Keywords

Traumatic brain injury; blood-brain barrier; neuroinflammation; brain edema

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Author Contributions

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Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability in children and adults in the developed world, accounting for over 10 million hospitalizations and an excess of $200 billion each year on a global scale (Pearn et al., 2017; Sorby-Adams, Marcoionni, Dempsey, Woenig, & Turner, 2017; Winkler, Minter, Yue, & Manley, 2016). In the United States alone, an estimated 1.7 million persons have a TBI event, resulting in over 50,000 deaths annually (Pearn et al., 2017; Prakash & Carmichael, 2015; Sorby-Adams et al., 2017). The Centers for Disease Control and Prevention estimates that 3.2 – 5.3 million persons in the United States are living with a TBI-related disability, a population that is twice as likely to die in 3.5 years after injury compared to persons in the general population of similar age, sex and race (Faul, Xu, Wald, Coronado, & Dellinger, 2010; Prevention, 2015). Furthermore, the persisting health effects of TBI can cause devastating functional limitation and reduced quality of life. This can include cognitive decline as well as disturbances involving memory, attention, behavior, and emotion. These patients also carry an increased risk for neurodegenerative disorders, mood disorders and post-traumatic epilepsy (Faul et al., 2010; Hart et al., 2012; Prevention, 2015; Riggio, 2011; Z. G. Wang et al., 2016).

TBI is an alteration in brain function or evidence of brain pathology as a result of rapid acceleration and deceleration that produces brain movement within the skull or an external head impact injury (Sorby-Adams et al., 2017; Winkler et al., 2016). For all age groups, the leading causes of TBI are motor vehicle crashes, suicides, falls, and assaults (Faul et al., 2010; Prevention, 2015). The resulting severity of the injury is dependent on a number of factors, including the nature of the initiating force, impact site, and magnitude (Sorby-Adams et al., 2017). The consequences of TBI, however, are not confined to the original event.

The injury that occurs in TBI can be separated into a primary mechanical injury and a delayed secondary injury involving a variety of changes at the cellular and molecular level (Salehi, Zhang, & Obenaus, 2017). The initial mechanical injury is a widespread shearing, tearing, or stretching of axons, referred to as axonal injury, as well as contusions, hemorrhages, and lacerations (Nikolian et al., 2018; Salehi et al., 2017; Sorby-Adams et al., 2017; Winkler et al., 2016). In the following hours to days, the secondary injury evolves as a result of neuronal and glial dysfunction, metabolic changes, neuroinflammation, cerebral edema and release of various signaling and inflammatory molecules from neuronal, glial and immune cells (Nikolian et al., 2018). This leads to a wide array of physiologic phenomena including blood-brain barrier (BBB) disruption, hypoperfusion, mitochondrial dysfunction, and oxidative injury in addition to several other mechanisms (Nikolian et al., 2018; Winkler et al., 2016). Therefore, the secondary injury can be more devastating than the primary injury, but also provides potential targets for therapeutic interventions.

The primary, sudden injury in TBI occurs as a direct result of impact and therefore cannot be treated. The focus then remains on preventative measures to possibly reduce the incidence of these events. The timeline and pathophysiology of the delayed, secondary injury, however, allows for a window of possible therapeutic options. While many advancements have been

made in understanding the inflammatory modulators and signaling pathways that mediate cellular damage in TBI, studies are still largely confined to preclinical models that are difficult to replicate in patient populations. Current TBI models are only able to show a fraction of the overall pathophysiology given the unpredictable nature of the inciting traumatic events (Pearn et al., 2017). The purpose of this review is to outline the pathophysiological mechanisms that occur in TBI and present the recent advancements made in understanding the neuroinflammatory processes and potential for therapeutic targets.

Pathophysiology

The primary injury in TBI occurs at the moment of impact and results in mechanical disruption of cellular integrity, ranging anywhere from subclinical to mild to moderate to severe injury. Subclinical and mild injury is due to stretching of the cellular membrane, resulting in rapid, unregulated influx of sodium (Na^+), efflux of potassium (K^+) and increases in intra-axonal calcium (Ca^{2+}) (Pearn et al., 2017; Wolf, Stys, Lusardi, Meaney, & Smith, 2001; Zetterberg, Smith, & Blennow, 2013). Increases in intra-axonal Ca^{2+} activates a protease, calpain, triggering calpain-mediated proteolysis of cytoskeletal proteins leading to irreversible axonal pathology (Saatman, Creed, & Raghupathi, 2010; Zetterberg et al., 2013). Additionally, increases in Ca^{2+} leads to activation of *N*-methyl-$_D$-aspartate (NMDA) receptors and further depolarization of neurons. Continuing activation of membrane pumps to restore ionic homeostasis leads to rapid glucose consumptions, depletion of energy stores, influx of Ca^{2+} into mitochondria, altered oxidative metabolism, and lactate production, resulting in acidosis and edema (Barkhoudarian, Hovda, & Giza, 2016; Giza & Hovda, 2014; Zetterberg et al., 2013).

In addition to ionic mechanisms, rapid acceleration and deceleration upon impact results in a widespread shearing of axons known as diffuse axonal injury. Ultrastructural analysis of axons following an injury shows sudden breakage and buckling of microtubules, ultimately ending in a progressive disassembly of microtubules (Tang-Schomer, Patel, Baas, & Smith, 2010). This is most characteristically located in the deep gyri at the grey and white matter interface and correlates with advanced magnetic resonance imaging (MRI) techniques to show the extent of disease (Zetterberg et al., 2013). The structural damage leads to an accumulation of protein products, interruption of axonal transport, axonal swelling, and degeneration (Tang-Schomer et al., 2010). This pathology is classically seen as singular axonal retraction bulbs and axonal varicosities, representing complete axonal disconnection (Johnson, Stewart, & Smith, 2013). While these physiologic disruptions are observed across the spectrum of severity for TBI, moderate to severe TBI is often associated with cranial vault fractures, hemorrhages, hematomas, and gross destruction of intracranial tissue. Ongoing hemorrhage and brain edema leads to mass effect and anatomical herniation of intracranial structures, further perpetuating neurological injury through axonal stretch and/or vascular disruption (Winkler et al., 2016).

Neuroinflammatory Response

In addition to the mechanisms that occur in the primary injury to neurons and axons, damage to glial cells, endothelial cells, and components of the BBB initiate many of the pathways implicated in TBI over a timeline of hours to days. The BBB is a specialized, selectivelypermeable barrier that is crucial in maintaining homeostasis within the brain's biochemical environment. It is composed of endothelial cells connected to an integrated vascular system by intercellular tight junctions, adherens junctions, pericytes, astrocytes, and the basement membrane (Alluri et al., 2016; Y. L. Liu et al., 2017; Sorby-Adams et al., 2017). A key component is the vasogenic edema that occurs as a result of BBB destruction and hyperpermeability. With disruption of the BBB, extravasation of plasma-derived factors and immune cells accumulate in the extracellular space, increasing total brain volume. This increase in extracellular oncotic pressure further perpetuates the process and can result in disastrous increases in intracranial pressure, changes in cerebral blood flow, tissue swelling, and cerebral herniation (Winkler et al., 2016). Furthermore, the build-up of protein-rich fluids containing plasmin, thrombin, fibrin, and free iron in the extracellular environment exposes the BBB to additional pro-inflammatory factors.

One mechanism that has been implicated in BBB breakdown is the upregulation of aquaporin 1 (AQP1) and 4 (AQP4) on endothelial cells, leading to increased water transport across the cell (Y. L. Liu et al., 2017). AQP4 is located at the basolateral membrane of ependymal cells and astrocyte foot processes. Injury in TBI leads to passive diffusion of free water through AQP4 channels in astrocytes (Winkler et al., 2016). Additional studies have implicated the relationship of rapidly increasing transforming growth factor beta 1 (TGF-β1) levels and enhanced BBB permeability in the cortex following TBI, in part because of a reduction of the tight junction protein, claudin-5, at the BBB (Prakash & Carmichael, 2015; Sorby-Adams et al., 2017; Winkler et al., 2016). Genetically altered mice lacking claudin-5 have demonstrated a hyperpermeable and compromised BBB, dying shortly after birth (Abbott, Patabendige, Dolman, Yusof, & Begley, 2010). Similarly, injured astrocytes have increased uptake of albumin via the TGF-β receptor, further contributing to electrolyte and water imbalances (Pearn et al., 2017).

Ultimately, as the BBB is disrupted in TBI, circulating macrophages, neutrophils, and lymphocytes are recruited to the injured sites to further potentiate inflammation. Injured brain parenchyma upregulate the expression of leukocyte adhesion molecules on the brain endothelium early in TBI (Worthylake & Burridge, 2001). The mechanisms by which leukocytes further disrupt the BBB include the generation of reactive oxygen species (ROS), activation of proteolytic enzymes, and secretion of cytokines and chemokines (Chodobski, Zink, & Szmydynger-Chodobska, 2011; Winkler et al., 2016). Furthermore, released chemokines attract additional inflammatory cells and allow for their extravasation across the vascular membrane.

The role of microglia in the neuroinflammatory response to TBI has been extensively studied. Microglia are a component of the primary innate immune system within the CNS and, under normal physiological conditions, constantly monitor the microenvironment for noxious stimuli and infectious processes (Nimmerjahn, Kirchhoff, & Helmchen, 2005). In response to injury, microglia become dysregulated and undergo dramatic changes in cell

morphology and function. They express various receptors and molecular patterns to respond to glutamate, ATP, growth factors, and cytokines that are released by surrounding cells, including other dysregulated microglia (Kumar & Loane, 2012). Among these, are pro-inflammatory substances, such as interleukin (IL)-1β, interferon-γ (IFNγ), tumor necrosis factor-α (TNFα), nitric oxide and ROS (Aungst, Kabadi, Thompson, Stoica, & Faden, 2014; Kumar & Loane, 2012). Interestingly, antiinflammatory substances (IL-4, IL-13, prostaglandins, and neutrophins) are also released (Pearn et al., 2017). Previous studies have identified multiple activation phenotypes of microglia within the CNS. Substances that are pro-inflammatory in nature enhance the M1 phenotype of microglia, leading to higher levels of pro-inflammatory cytokines and ROS (Kumar & Loane, 2012). The end result is ideal for basic host defense but ultimately damages healthy tissue as well. Those anti-inflammatory substances have been shown to activate the M2 phenotype of microglia, promoting neurite growth and extension, angiogenesis, tissue repair and suppression of harmful immune responses (Butovsky, Talpalar, Ben-Yaakov, & Schwartz, 2005; Colton et al., 2006; Kigerl et al., 2009; Ponomarev, Maresz, Tan, & Dittel, 2007). Literature suggests simultaneous activation of both of these phenotypes, but the mechanisms to favor one over the other is still largely unknown (Kigerl et al., 2009; Kumar & Loane, 2012). Moreover, the M1/M2 classification has become quite controversial in literature as it oversimplifies the complexity of the CNS microglia response in vivo. Data suggests both phenotypes are typically present in vivo conditions and able to reversibly change its phenotype or function in response to external stimuli (Kigerl et al., 2009; Stout & Suttles, 2004).

Another key component of the neuroinflammatory state in TBI is the group of matrixins known as matrix metalloproteinases (MMPs). MMPs are zinc-dependent proteases that participate primarily in the degradation of the extracellular matrix (ECM) (Nakase et al., 2006). Under normal physiologic conditions, MMPs have a significant role in growth, development, wound healing, neurogenesis, angiogenesis, and bone remodeling. In neurological diseases, including TBI, MMPs have been shown to cause BBB disruption, neuroinflammation, hemorrhage and cell death (Abdul-Muneer, Pfister, Haorah, & Chandra, 2016). MMP upregulation leads to disruption of BBB tight junction proteins such as claudin-5 and occludin, leading to BBB hyperpermeability and vasogenic edema. They also activate vascular endothelial growth factor (VEGF), which in turn activates caspase-1 leading to cell apoptosis. Furthermore, they convert many other pro-caspases into active caspases to induce cell apoptosis (Abdul Muneer, Alikunju, Szlachetka, & Haorah, 2012; Abdul-Muneer et al., 2013; Rosenberg et al., 2001; Yang, Estrada, Thompson, Liu, & Rosenberg, 2007).

There are several classes of MMPs, each responding to certain growth factors and cytokines. In TBI, MMPs are activated by signaling substances such as ROS and inflammatory cytokines, including TGF-β, IL-1β and TNFα (Haorah et al., 2007; Hsieh, Wang, Wu, Chu, & Yang, 2010). MMPs are typically secreted by astrocytes, endothelial cells, neurons, microglia, pericytes, and circulating leukocytes (Abdul-Muneer et al., 2016; Nagase, Visse, & Murphy, 2006; Yong, 2005). Of those MMPs upregulated in TBI, animal studies have identified MMP-2, MMP-3, and MMP-9 as being key in the pathophysiology of TBI, including influencing neuroinflammation and cell death (X. Wang, Mori, Jung, Fini, & Lo, 2002). MMP-2 and MMP-9 belong to a group of enzymes known as gelatinases whose

function is to digest type I, II, and III collagens as well as gelatins. They are often found within the ECM, cerebrospinal fluid (CSF), and serum (AbdulMuneer et al., 2016). MMP-3, also known as stromelysin 1, has proteolytic properties for digesting the ECM as well as the ability to process a number of zymogen pro-MMPs into their active MMP forms (Nagase & Woessner, 1999). Therefore, MMPs can influence TBI pathophysiology via numerous mechanisms.

An integral aspect of the neuroinflammation in TBI is the oxidative stress from generated ROS in several of the mechanisms described above. These ROS and their derived highly reactive free radicals, such as superoxide radical, can induce peroxidation of membrane lipids and compromise the BBB (Hall, Vaishnav, & Mustafa, 2010). The vasodilatory factor nitric oxide, released by several neuroinflammatory mechanisms, contributes to the formation of a variety of free radicals by reacting with superoxide (Beckman, 1991). The CNS itself is very sensitive to free radical-induced peroxidation given its high concentrations of peroxidation-susceptible membrane lipids such as arachidonic acid, linolenic acid, docosahexaenoic acid and linoleic acid (Hall et al., 2010). Furthermore, several studies have demonstrated an increase in BBB permeability as well as degradation of tight junction proteins after exposure to ROS (Fischer, Wiesnet, Renz, & Schaper, 2005; Schreibelt et al., 2007).

Potential Therapeutic Interventions

Preclinical TBI Models

Given the unpredictable mechanisms and severity of injury in TBI, study design remains a challenge in preclinical observation. Preclinical animal models have increased in recent years given their ability to replicate certain biomechanical, molecular, and cellular aspects of human TBI (Xiong, Mahmood, & Chopp, 2013). Various models have been developed to replicate TBI, often involving rodents due to their relative cost, size, and ability to standardize outcome measurements (Gurdjian, Lissner, Webster, Latimer, & Haddad, 1954; Xiong et al., 2013). However, animal models inherently provide a homogenous, preset group of parameters that may not be able to fully encapsulate every aspect of injury that occurs in human TBI (Marklund, Bakshi, Castelbuono, Conte, & McIntosh, 2006). Nonetheless, animal models have improved in recent years and have demonstrated promising results regarding the delayed, secondary neuroinflammatory state of TBI. Of the animal models that exist, four specific models are widely used in literature. These are the controlled cortical impact injury (CCI), weight drop-impact acceleration injury, fluid percussion injury (FPI), and blast injury (Cernak et al., 1996; Dixon, Clifton, Lighthall, Yaghmai, & Hayes, 1991; Dixon et al., 1987; Lighthall, 1988; Marmarou et al., 1994; Xiong et al., 2013).

As mentioned previously, IL-1β is one of many pro-inflammatory cytokines involved in the neuroinflammatory state of TBI. Multiple studies have demonstrated that inhibition of IL-1β activity attenuates cerebral edema and delayed injury in TBI. Clausen et al. used mice models treated with an IL-1β neutralizing antibody that were subjected to a CCI injury. They successfully demonstrated a reduction in lesion volume, hemispheric tissue loss, cognitive deficits, microglial activation, and cortical infiltration at post-TBI day 7 when compared to control antibody treatment (Clausen et al., 2009). Jones et al. showed similar results in mice

treated with recombinant mouse IL-1 receptor antagonist following cryogenic aseptic cerebral injury. They highlighted the IL-1 receptor antagonist's effects on reducing the number of nitric oxide synthase (NOS)-2 positive cells, which normally produce high levels of cytotoxic nitric oxide in traumatic injury (Jones et al., 2005).

More recently, it has been shown that IL-1β release, among other cytokines, predominantly mediated by nucleotide-binding oligomerization domain (NOD)-like receptor pyrin domaincontaining 3 ($NLRP_3$) inflammasome (H. D. Liu et al., 2013). Preclinical studies aimed at genetically or pharmacologically inhibiting $NLRP_3$ inflammasome activity reduced the inflammatory response in TBI and improved neurological outcomes (Fann et al., 2013; Ma et al., 2014). Additionally, the renin-angiotensin system has been implicated in neuroinflammation and neurodegenerative disorders in the past. More specifically, angiotensin II signaling was involved in many of the mechanisms in TBI, possibly due to decreased cerebral blood flow, sympathetic overdrive and inflammation after activation (Villapol, Balarezo, Affram, Saavedra, & Symes, 2015). Wei et al. went on to study the angiotensin receptor blocker (ARB) telmisartan, a highly lipid-soluble ARB able to penetrate brain tissue, and its effects on $NLRP_3$ and IL-1β induced inflammation (Wei, Hu, Zhang, Yao, & Mao, 2016). They reported that telmisartan pretreatment significantly attenuated the cerebral edema induced by TBI when compared to the non-treated group, using brain water content as a sensitive measure. They also showed that prophylactic telmisartan therapy significantly reduced BBB damage, activation of $NLRP_3$, and IL-1β maturation. Telmisartan also decreased levels of other inflammatory mediators such as caspase1, apoptotic speck-containing protein, and IL-18 (Wei et al., 2016).

Additional studies have demonstrated the potential therapeutic effects involved in the mechanisms involving IL-1β and calpains. As previously discussed, calpains are non-lysosomal, cysteine or thiol proteases that are activated by Ca^{2+} and serve to cleave proteins involved in many cellular functions (Bralic & Stemberga, 2012). Sustained activation of calpains has also been associated with neuronal death following CNS trauma, ischemia, and spinal cord injury (Alluri et al., 2016; Bralic & Stemberga, 2012; Saatman et al., 2010; Zhao et al., 2016). In addition to Ca^{2+} levels, Calpain inhibitors such as calpastatin, also regulate calpain activation under normal physiologic conditions. Increases in calpain expression are seen in injured endothelial cells at the BBB, suggesting a relationship with alterations in BBB permeability (Bralic & Stemberga, 2012). Alluri et al. examined the role of calpains in BBB dysfunction and hyperpermeability in the context of TBI (Alluri et al., 2016). Mice were subjected to CCI injury, and microvascular endothelial cell monolayers were exposed to calpain inhibitor III and calpastatin. Interestingly, inhibition of calpain both significantly attenuated IL-1β induced calpain activity and IL-1β induced BBB tight junction dysfunction (Alluri et al., 2016). Thus, calpain inhibition can diminish BBB hyperpermeability in TBI by preventing disorganization of the BBB tight junctions and cytoskeletal assembly (Alluri et al., 2016).

Another proposed therapeutic strategy is the use of a protective signaling molecule, progranulin, which is often released from neurons and microglia (Menzel et al., 2017). Progranulin (known as granulin epithelin precursor or PC-cell-derived growth factor) is an autocrine growth factor that is present in rapid cycling cell lineages and cancers (Tang et al.,

2011). It functions in a variety of pathologies, with critical roles in wound healing, inflammation, and host defense (He, Ong, Halper, & Bateman, 2003; Kessenbrock et al., 2008; Zhu et al., 2002). Genetic alterations in progranulin function have also been associated with a variation of frontotemporal lobar degeneration and Alzheimer disease (Baker et al., 2006; Perry et al., 2013). Interestingly, progranulin has been shown to be a ligand of the TNFα receptor, competing with and antagonizing TNFα mediated inflammatory processes (Tian, Zhao, & Liu, 2014; Zhao et al., 2016). Furthermore, Kanazawa et al. demonstrated the neuroprotective effects of progranulin in mice models with acute focal cerebral ischemia. In their studies, progranulin regulated vascular permeability via VEGF and suppressed inflammatory changes following an ischemic event through IL-10, an anti-inflammatory cytokine (Kanazawa et al., 2015). Menzel et al. went on to study the inflammatory phase of TBI on progranulin-deficient mice that were subjected to a CCI injury. In their study, they found that when compared to the wild-type mice, progranulindeficient models had increased transcription of pro-inflammatory TNFα, IL-1β, and IL-6 as well as decreased transcription of IL-10, signifying an increase inflammation (Menzel et al., 2017). Additionally, progranulin-deficient mice had markedly increased astrogliosis at day 5 post-TBI when compared to the control. Recombinant progranulin administration in progranulin-deficient mice following TBI significantly reduced neurological deficits by day 5, restoring normal levels of inflammatory cytokine transcription (Menzel et al., 2017).

Several growth factors have been proposed in literature as potential therapeutic targets for TBI and/or BBB disruption. One recent example is basic fibroblast growth factor (bFGF), a growth factor expressed in high numbers in the nervous system where it serves multiple functions including the regulation of BBB integrity (Murakami et al., 2008; Zhang et al., 2013). Wang et al. studied the effects of exogenous bFGF on the BBB in TBI mice models subjected to a weight drop-impact injury (Z. G. Wang et al., 2016). Their in vivo and in vitro studies both demonstrated that bFGF was neuroprotective and prevented BBB dysfunction by upregulating claudin-5, zonula occludens-1 (ZO-1), and occludin among several tight junction proteins (Z. G. Wang et al., 2016).

Investigators have also attempted to demonstrate the therapeutic potential of several natural compounds in TBI. One such group of compounds are known as catechins, polyphenolic flavonoids found in large concentrations in green tea. Catechins have demonstrated antioxidant and anti-inflammatory properties in a variety of diseases including Parkinson's, Alzheimer's, and Huntington's diseases as well as amyotrophic lateral sclerosis (ALS) (Mandel, Amit, Weinreb, Reznichenko, & Youdim, 2008). Catechins have also been promising in attenuating the inflammatory response in cerebral ischemia (Ashafaq et al., 2012). Jiang et al. examined the mechanistic effect of catechins in male rats subjected to a CCI TBI (Jiang, Zhang, Cai, Huang, & You, 2017). Catechin-treated TBI rats had a significant dose-dependent reduction in brain water content when compared to the control, indicating a prevention of BBB dysfunction (Jiang et al., 2017). Furthermore, catechin-treated mice had higher mRNA expression and protein levels of tight junction proteins (occludin and ZO-1) than the control (Jiang et al., 2017). Catechin treatment also resulted in a decrease in pro-inflammatory factors such as IL-1β, IL-6 and iNOS as well as increases in anti-inflammatory arginase 1 (Jiang et al., 2017). Cordycepin (3'deoxyadenosine) is another such compound, isolated from the fungal species *Cordyceps militaris*, that has exhibited

anti-inflammatory and anti-oxidant effects in literature (Park et al., 2014). Notably, studies have shown that cordycepin inhibits the release of several proinflammatory substances including TNFα and IL-1β while also increasing many antiinflammatory cytokines (Tuli, Sharma, Sandhu, & Kashyap, 2013). Yuan et al. demonstrated the anti-inflammatory properties of cordycepin in rats subjected to a CCI injury (Yuan et al., 2016). They reported lower neurological severity scores, less brain water content, and smaller brain infarct volumes in cordycepin-treated TBI models when compared to the untreated group. They also found that cordycepin treatment resulted in an increase in tight junction proteins, an increase in arginase 1, and a decreased expression of IL-1β, iNOS, and MMP-9 in TBI models (Yuan et al., 2016).

In recent years, certain existing pharmacological agents have demonstrated promising results as preclinical studies in the treatment of TBI evolve. The investigation of ω−3 fatty acids such as docosadexaenoic acid (DHA) was performed in mild TBI. The available evidence suggests that ω−3 fatty acid levels are decreased after a mild TBI and that supplementation may ameliorate a degree of structural and oxidative damage that occurs in the period after injury (Barrett, McBurney, & Ciappio, 2014). Separate studies examined BBB integrity following the treatment of fresh frozen plasma (FFP) and valproic acid in swine TBI models (Nikolian et al., 2018). Interestingly, both FFP treatment alone as well as combination FFP and valproic acid therapy resulted in increased expression of tight junction proteins essential for BBB integrity when compared to normal saline treatment. Furthermore, their studies suggested a synergistic effect when FFP and valproic acid are used in combination (Nikolian et al., 2018). Lastly, there are distinct studies now analyzing minocycline, a tetracycline antibiotic that cross the BBB, and Nacetylcysteine, an antioxidant, in combination for the management of TBI (Abdel Baki, Schwab, Haber, Fenton, & Bergold, 2010; Haber et al., 2013; Sangobowale et al., 2018). Such studies have demonstrated both anti-inflammatory and BBB integrity-sparing properties of the two, through many of the same mechanisms discussed in this section (Abdel Baki et al., 2010; Haber et al., 2013; Pearn et al., 2017; Sangobowale et al., 2018).

Recent Clinical Trials

While numerous preclinical studies demonstrate promising results in the management of TBI, researchers have yet to successfully translate these clinically. In fact, since 1993, there have been over 30 failed clinical trials for TBI that were initially supported by extensive preclinical studies (Samadani & Daly, 2016). These include studies involving hypertonic saline, prostacyclin, progesterone, hypothermia, and temperature control as well as several pharmacological therapies (Samadani & Daly, 2016). This could be due in part to the inability of predicting or replicating the exact kinetics in injury despite having multiple brain injury models. Additionally, many of the pharmacokinetics and cellular mechanisms within the brain that interplay in TBI are largely unknown by investigators. Nonetheless, there are a handful of recent clinical studies that will be discussed in this section that further our understanding of TBI.

Amantadine, approved for use in Parkinson’s disease, has known antagonist activity at NMDA receptors within the CNS as well as other less known dopaminergic effects (Kim et

al., 2018). The use of amantadine in the subacute phase in moderate to severe TBI has been reported in a group of trials over recent years. In a randomly assigned crossover trial, a group of thirty-five patients with initial Glasgow Coma Scale (GCS) score of less than or equal to 10 were given amantadine for six weeks after injury. After the first three months of injury, participants taking amantadine were found to have a more rapid functional recovery as seen from an improvement in Glasgow outcome scale (GOS) scores, Disability Rating Scores (DRS), Mini-Mental Status exam (MMSE) scores, and functional independence measure (FIM) cognitive scores (Meythaler, Brunner, Johnson, & Novack, 2002). In another such study of TBI patients who were in a vegetative or minimally conscious state for four to sixteen weeks after initial injury, patients were randomly assigned into two groups, one of which received a four-week course of amantadine. In the group of patients receiving amantadine versus placebo, patients exhibited accelerated functional recovery as seen from lower DRS scores with no significant differences in adverse advents (Giacino et al., 2012). Sprtizer et al. similarly conducted a multicenter, randomized controlled trial, in which one hundred and eighty-four patients were divided. Over a four-week trial, half the patients received amantadine. The rate of recovery was found to be accelerated in patients receiving amantadine, as evidenced by a lower DRS score when compared to controls (Spritzer et al., 2015). In addition to functional recovery, amantadine has also been studied on patients with TBI greater than or equal to 6 months ago who suffer from irritability. Eighty-two patients participated in taking amantadine twice daily for sixty days. Although patients taking amantadine reported improved irritability, the observer perspective on these patients did not reveal differences in irritability between control and study groups (Hammond et al., 2015).

Another potential therapeutic intervention is the use of the glycoprotein erythropoietin (EPO). EPO has demonstrated neuroprotective effects through several anti-inflammatory and antioxidant effects in preclinical studies, but it has since shown mixed results in recent clinical trials (Pearn et al., 2017). In a recent randomized controlled clinical trial by Li et al., one hundred and fifty-nine patients with severe TBI were divided. Of these, seventy-nine patients received five total subcutaneous injections of human EPO after a severe TBI. Patients receiving EPO therapy revealed lower levels of two common serum biomarkers present in TBI patients – neuron specific enolase and S-100β. Furthermore, more patients receiving EPO injections had higher GOS scores at three-months post injury without an increase in severe infections or thromboembolic events when compared to control patients (Li et al., 2016). In other clinical trials involving EPO, the results were not as promising. In a clinical trial by Bai et al., one hundred and twenty patients with severe TBI were randomly divided. Of these, sixty patients received five subcutaneous doses of EPO. At the end of ten weeks, patients receiving EPO therapy showed no significant differences in GOS scores nor mortality (Bai & Gao, 2018). Furthermore, Nichol et al. tested the effects of EPO on three hundred and eight TBI patients by providing three subcutaneous injections of EPO over a course of three weeks. Their results indicated patients receiving EPO injections did not show a significant difference in GOS scores, mortality, or deep venous thromboembolism of the lower extremities (Nichol et al., 2015).

Worth mentioning as well is the use of tranexamic acid (TXA) in both ICH and TBI. TXA is a synthetic lysine derivative that competitively blocks the lysine-binding sites on plasminogen, inhibiting its activation and binding to fibrin, resulting in a reduction of

fibrinolysis. TXA also inhibits tissue plasminogen activator (Hunt, 2015). It has been widely studied in literature due to its involvement in fibrinolysis. Its role, however, in ICH and TBI as a treatment modality has been unsuccessful. In a randomized controlled trial, two hundred and thirty-eight patients with severe TBI (GCS 4 – 12) were randomized into two groups, with one group of patients receiving a loading dose of TXA followed by a maintenance dose of TXA. Compared to patients who did not receive TXA, there was no significant difference in the reduction of progressive ICH on repeat CT scans, patient outcomes, mortality, nor differences in thromboembolic events (Yutthakasemsunt et al., 2013). Similarly, in a nested, randomized controlled trial, half of the two hundred and seventy enrolled patients were given a TXA loading dose and maintenance dose within eight hours of a severe TBI. The results of this study did not show a clinically significant improvement in clinical outcomes (Crash-2 Collaborators, 2011). However, a pooled analysis of these two randomized controlled trials revealed a significant reduction in intracranial hemorrhage with TXA and a non-statistically significant change in clinical outcomes in patients with TBI (Zehtabchi, Abdel Baki, Falzon, & Nishijima, 2014). Most recently, in a randomized controlled trial of TBI patients with any kind of blood present on initial CT Head, one hundred and forty-nine patients were divided into two groups, with one group receiving TXA. After twenty-four hours, repeat CT head was taken to determine if TXA administration could slow the progression of hemorrhagic lesion growth. Administration of TXA did not lead to significant prevention of post-traumatic hemorrhagic lesions or improved clinical outcomes (Fakharian, Abedzadeh-Kalahroudi, & Atoof, 2018).

Conclusion

TBI remains a leading cause of death and disability in the developed world despite the recent advancements made in medicine. Patients who survive the initial injury often suffer from a variety of neurocognitive disorders and have a significantly reduced quality of life. It is evident that a gap still exists between the preclinical TBI model and clinical practice. The goal of this review has been to 1) highlight the pathophysiology of TBI, both in primary and secondary event and 2) discuss several preclinical and clinical studies that further our understanding of the role of neuroinflammatory in TBI. The current understanding of TBI and its pathophysiology at a molecular level has shown promise for novel therapeutic treatments focused on targeting several mechanisms responsible for inflammation and BBB disruption. Nonetheless, further research into the mechanisms and therapeutic targets of TBI are needed to improve patient outcomes and lessen the societal burden.

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Significance Statement:

This review focuses on the mechanisms involved in traumatic brain injury, separating them into a primary phase and delayed, secondary phase. Several inflammatory mechanisms have been isolated in the hours to days following a traumatic brain injury that intimately interplay with disruption of the blood-brain barrier. Several preclinical studies that isolate these mechanisms are presented here to show potential therapeutic targets that could attenuate this inflammatory response. The current state of traumatic brain injury clinical trials is discussed, stressing the need of further investigation in hopes for the development of novel therapeutic strategies.