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Traumatic Brain Injury: Mechanistic Insight on Pathophysiology and Potential Therapeutic Targets

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Abstract

Traumatic brain injury (TBI) causes brain damage, which involves primary and secondary injury mechanisms. Primary injury causes local brain damage, while secondary damage begins with inflammatory activity followed by disruption of the blood–brain barrier (BBB), peripheral blood cells infiltration, brain edema, and the discharge of numerous immune mediators including chemotactic factors and interleukins. TBI alters molecular signaling, cell structures, and functions. Besides tissue damage such as axonal damage, contusions, and hemorrhage, TBI in general interrupts brain physiology including cognition, decision-making, memory, attention, and speech capability. Regardless of the deep understanding of the pathophysiology of TBI, the underlying mechanisms still need to be assessed with a desired therapeutic agent to control the consequences of TBI. The current review gives a brief outline of the pathophysiological mechanism of TBI and various biochemical pathways involved in brain injury, pharmacological treatment approaches, and novel targets for therapy.

Keywords Traumatic brain injury · Excitotoxicity · Mitochondrial dysfunction · Oxidative stress · Neuroinflammation · Apoptosis · Nuclear factor-kappa B (NF-κB)

Introduction

Traumatic brain injury (TBI) arises due to any exterior mechanical force that leads to a temporary or permanent impairment of physical, psychological, and cognitive function along with an altered state of consciousness (Maxwell 2012; Zhao et al. 2011). TBI symptoms include dizziness, headaches, amnesia, and nausea that may improve within days to weeks of insult, but severe injury may lead to long-term behavioral and cognitive defects (Van Gils et al. 2020; Yamamoto et al. 2018). Fragments of evidence have shown increased incidence of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and chronic traumatic encephalopathy caused by head trauma (Safinia et al. 2016). TBI treatment, which may involve pharmacotherapy, cognitive therapy, or surgical options such as bilateral decompressive craniectomy, varies according to the severity of injury (Stocchetti et al. 2017). This review summarizes molecular and cellular events involved in the pathogenesis of TBI. Potential drug targets that are updated in this review need to be explored to develop a novel treatment for TBI.

Methodology: A literature review of PubMed, Medline, Bentham, Scopus, and EMBASE (Elsevier) databases was conducted using the keywords "traumatic brain injury," excitotoxicity," "mitochondrial dysfunction," "oxidative stress," "neuroinflammation," and "apoptosis." These keywords were used to gather the latest articles to explore the nature of the extensive work on various mechanistic approaches and therapeutic modulations related to TBI.

Epidemiology

In young adults, TBI has become a significant cause of death and disability, particularly in an urbanized world, such as in the UK, where 1.4 million individuals suffer head injuries per year, with increasing incidence in low-income countries (Hyder et al. 2007). The Word Health Organization (WHO) estimated that traffic accidents and TBI represent the third most common cause of mortality worldwide. TBI results

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in significant health and socioeconomic problems (Maas et al. 2008). A meta-analysis in 16 European countries estimated 262 cases per 100,000 individuals of hospital-admitted TBIs (Peeters et al. 2015, 2017). Recently, 2.5 million TBI cases were reported in the European Union, with 90% mild cases (Foks et al. 2017). In the United States, 52,000 deaths annually due to TBI have been reported. The National Institutes of Health Consensus estimated that 2.5–6.5 million Americans have TBI-associated disabilities (Khajavikhan et al. 2016). Using data from a national trauma databank, Rosenfeld et al. found that TBI was the most widespread non-accidental trauma (NAT) in the United States. Between 2007 and 2014, 678,503 children under 15 years of age were admitted to the hospital for traumatic injuries, 3% of whom had NAT; among these, 50% were diagnosed with TBI. A study in the UK reported that head injury (HI) accounted for 3.4% of all hospital admissions, and 453/100,000 emergency department visits were due to TBI. In Nigeria, 2710/100,000 visits per year in an accident and emergency department (AED) were for TBI. India has the second largest population and more than a quarter of trauma deaths in the world. The national crime record bureau reported a 63% increase in accident-related deaths during the period 2004–2013 in India, out of which 50% were trauma-associated. Data have been published on 20,000 TBI patients, representing only a fraction of the total number of TBI patients in India each year. An epidemiological study in Bangalore revealed incidence, mortality, and case fatality rates of 150/100,000, 20/100,000, and 10%, respectively (Maas 2017).

Pathophysiology of TBI

The biochemical, cellular, and physiological events that occur during primary injury often progress to delayed and prolonged secondary damage, lasting from hours to years. Several factors contribute mechanistically to secondary injuries, including excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, neuroinflammation, axonal degeneration, and apoptotic cell death (Fig. 1).

Excitotoxicity

The destruction of the blood–brain barrier (BBB) caused by TBI results in the release of excess neurotransmitters and failure of glutamate transporters normally involved in the reuptake of the glutamate (Chamoun et al. 2010). Glutamate, along with its various metabolites, binds to glutamate receptors (both ionotropic and metabotropic) and activates them. The NMDA and AMPA receptors are members of the group of ionotropic glutamate receptors that allow sodium, potassium, and calcium ions into the membrane for depolarization (Brustovetsky et al. 2010). Excessive glutamate release in TBI conditions causes overexpression of these receptors and alters ion homeostasis by permitting extracellular Ca^{2+} and Na^{+} ions to enter the cell (Meldrum 2000). It has been shown that GluN2B is present in synaptic cytosol and is involved in mediating excitotoxic response (Wyllie et al. 2013). Excess intracellular Ca^{2+} triggers many downstream signaling molecules such as Ca^{2+}/calmodulin-dependent protein kinase II, protein kinase C, mitogen-activated protein kinases (MAPK), and protein phosphatases. Excessive Ca^{2+} in the cytosol leads to activation of apoptotic proteins such as calpain, calcineurin, and caspases that lead to cell death (Folkerts et al. 2007; Weber 2012). Mitochondrial function is also impaired due to accumulated reactive oxygen species (ROS). Excitatory neurotransmitters cause cells to die from oxidative stress, and excitotoxicity results in cell death (Chamoun et al. 2010). Immediately post-trauma, the shear and stretch forces due to head injury promote glutamate-independent excitotoxicity via NMDA receptor activation (LaPlaca and Thibault 1998). One study also demonstrated the mechanosensitivity of NMDA receptors regarding particular subunits and signaling cascades involved in regulating NMDA receptors in response to mechanical stimuli. The results showed the GluN2B subunit as a mediator of mechanosensitive response (Singh et al. 2012).

Mitochondrial Dysfunction

Mitochondrial impairment is a hallmark event of TBI that leads to alteration of physiological and metabolic function, ultimately causing cell death. The excessive influx of Ca^{2+} into mitochondria may result in ROS production and mitochondrial membrane depolarization without ATP synthesis (Susin et al. 1998; Xiong et al. 1999). The invasion of excess ions into mitochondria results in ROS production, mitochondrial membrane depolarization, and suppression of ATP synthesis (Singh et al. 2006). As a result, both the electron transport chain and oxidative phosphorylation processes are compromised, leading to dysfunction in calcium regulation and metabolic function (Naga et al. 2007). Under stress conditions, mitochondrial permeability transition pore (mPTP) is activated. Mitochondrial dysfunction also causes a structural change in the adenine nucleotide translocator protein upon binding with cyclophilin D. This leads to mPTP opening and increased inner membrane permeability (Naga et al. 2007). Further mitochondrial proteins such as apoptosis-inducing factor (AIF) and cytochrome c play a decisive role in apoptotic cell death (Tsujimoto and Shimizu 2007).

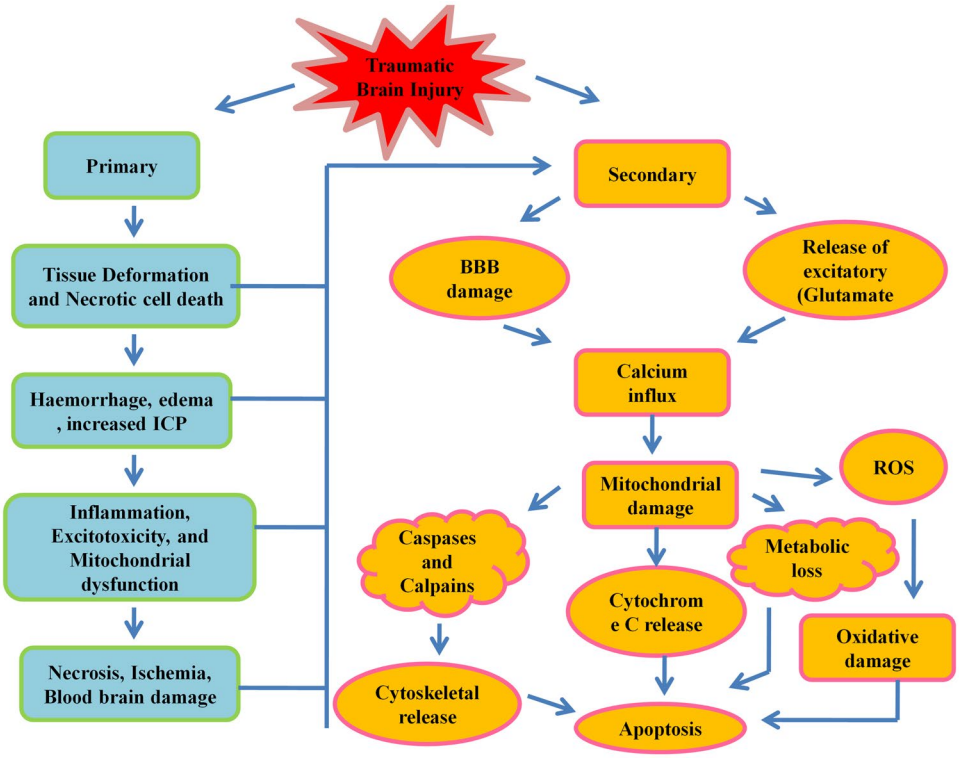

Fig. 1 The pathophysiological mechanism of primary and secondary brain injury

Oxidative Stress

Increased levels of free radicals, both reactive nitrogen species (RNS) and reactive oxygen species (ROS), can result from secondary cell death and oxidative stress. The mitochondrial function is disturbed due to the excessive ROS produced, causing mitochondrial membrane damage via lipid peroxidation (Sohahmi and Kohen 2011; Xiong et al. 1999). After TBI, there is increased ROS production from the electron transport chain (ETC) in response to the damaged cells. In contrast, Ca^{2+} accumulation after TBI aids in the production of NO by nitric oxide synthases (NOS) (Deng et al. 2007). Excessive NO reacts with free radical superoxide, forming peroxynitrite (PN), which further promotes oxidative damage. Besides their effects on proteins and DNA, these ROS also damage cell membranes by reacting with polyunsaturated fatty acids to form lipoperoxyl radicals (Ansari et al. 2008). Also, abnormal accumulation of intracellular Ca^{2+} ions has been associated with prolonged excitotoxicity. Specifically, the constant release of ROS and lipid peroxidation has an adverse effect on cerebral blood flow, which causes immunosuppression and brain plasticity (Shohami and Kohen 2011).

Neuroinflammation

TBI induces a multifaceted range of immunological/inflammatory tissue responses with similarities to ischemia/reperfusion injury. Primary and secondary processes individually activate cellular mediators comprising prostaglandins, pro-inflammatory cytokines, and free radicals (Plata-Salaman 2002; Werner and Engelhard 2007). Evaluation of cerebrospinal fluid, post-mortem tissue of TBI patients (Goodman et al. 2009; Frugier et al. 2010), and rodent models (Lotocki et al. 2009; Semple et al. 2010) revealed that polymorphonuclear leukocytes and cytokines released inflammatory mediators such as IL-6, IL-1β, and TNF-α 24 h post-trauma. The prolonged release of cytokines showed that the permeability of the BBB is altered, which leads to edema formation and neurological defects. TNF-α, being a member of the Fas family, interacts strongly with Fas ligand and activates caspases for programmed cell death (Bye et al. 2007). Chemokines, for example IL-8 (CXCL8), MIP-α, and MCP-1, have been observed in traumatized sites that recruit leukocytes to the site of injury. Further, endothelial and leukocyte cell adhesion molecules such as

ICAM-1 and VCAM-1 facilitate the recruitment of leukocytes and immune cells to the injured site by interacting with the endothelium (Frugier et al. 2010). In prolonged neuroinflammation, macrophages turn on microglial cells, increasing the release of astrocytes, which has been observed in TBI survivors many years after injury (Bye et al. 2007; Johnson et al. 2013). The role of GSK-3β in the physiological model of mild TBI (mTBI) had been studied at both the cellular and behavior levels. Glycogen synthase kinase-3 (GSK-3) β has shown inference in depressive behavior apart from regulating cell apoptosis. Shapira et al. evaluated the effect of GSK-3β inhibitor lithium or L803-mts in improving mTBI-induced depression (Shapira M et al. 2007).

Axonal Degeneration

A sudden mechanical injury to neurons results in diffuse axonal injury (DAI) that destroys the axonal cytoskeletal network, comprising microtubules and neurofilaments (Andriessen et al. 2010). Acute axonal damage due to trauma resulting from persistent calcium-mediated proteolysis is distinguished by myelin sheath degradation, axonal transport damage, and buildup of axonal transport proteins (Su and Bell 2016). An excessive increase in axonal transport proteins results in long-term swelling of axons and apoptosis of cells and oligodendrocytes (Fünfschilling et al. 2012). In a TBI experimental model, the hallmark of DAI was determined by axonal markers β-amyloid precursor protein (β-APP) and neurofilament (NF) 1 day post-TBI, and retraction bulbs were predominantly observed in the corpus callosum and pyramidal tracts of the brain stem. Their presence has been reported in the hippocampus, cingulum, and cortex (Hellewell et al. 2010; Lee and Ng 2019).

Apoptotic Cell Death

Neuronal apoptosis is the main characteristic of secondary brain injury, and in the human hippocampus, neuronal cell death is evident up to 1 year after TBI (Smith et al. 1997). Various downstream proteases such as calpain and caspases are activated by molecular pathways, for example, extracellular signal-regulated kinase (ERK), Janus kinase/signal transducer and activator of transcription (JAK/STAT); p38 MAPK, (Shim et al. 2007; Tan et al. 2006). Two pathways mediate apoptosis, the extrinsic pathways (EP) and the intrinsic pathways (IP). EP integrates TNF-Fas interactions with their respective cell receptors, whereas IP incorporates mitochondrial depolarization of cytochrome c emissions that activate downstream caspase 3 by caspase 8 and 9 modulation (Rossi and Gaidano 2003; Schmitz et al. 2000). In TBI, however, caspase-independent apoptosis leads to the release into the nucleus of mitochondrial proteins including AIF, Smac/DIABLO, endonuclease G, and polymerase-1, which further activates upstream signaling molecules for damage to neuronal and glial cells (Hasegawa et al. 2011; Raghupathi et al. 2000).

Pharmacological Treatment Approach for TBI

Anti-Excitotoxic Drugs

Treatment strategies for neuronal excitotoxicity in TBI have been discussed in various studies (Fig. 2). Shohami and Mechoulam showed that dexanabinol (HU-211) attenuated NMDA receptor-stimulated neurotoxicity in neuronal cultures (Shohami and Mechoulam 2000). In post-TBI, HU-211 reduced brain edema and aided in the repair of the BBB (Shohami et al. 1997), and was evaluated in a clinical phase III trial (NCT00129857). Correspondingly, MK-801 (dizocilpine), an NMDA antagonist, reduced oxidative stress, microglial activation, and neuronal cell death. Similarly, AMPA receptor antagonist NBQX attenuated damage to neuronal axons (Follett et al. 2000). Calcium channel blockers are used to inhibit the excessive calcium in the cytosol that contributes to excitotoxicity in secondary injuries in TBI. SNX-111 (ziconotide), a calcium channel inhibitor, reduced trauma-induced calcium accumulation in ipsilateral regions (Samii et al. 1999). Calcium channel inhibitor (S)-emopamil reduced cerebral blood flow and brain edema. Nimodipine (L-type voltage-sensitive calcium channel antagonist) was found to have a beneficial effect on rat memory impairment. However, it showed hypotensive effects in a clinical trial, which was then terminated (Hassan et al. 1999). Studies have also demonstrated that calpain inhibitor MDL-28170 suppressed damage to neurons in both hypoxic-ischemic injury and TBI by inhibiting caspase-3 and calpains (Thompson et al. 2010). The antiparkinsonian drug combinations of bromocriptine, amantadine, and levodopa with carbidopa demonstrated diverse mechanisms of action that eventually enhanced dopamine levels in the brain (Vijiaratnam and Foltynie 2020). Amantadine can increase dopamine discharge by acting presynaptically or inhibiting its reuptake; it also alters the dopamine receptor configuration by acting postsynaptically. It may protect from glutamate-induced excitotoxicity by acting noncompetitively on NMDA receptor antagonists (Tan et al. 2015). Amantadine (250 mg) and bromocriptine (5 mg) administered twice a

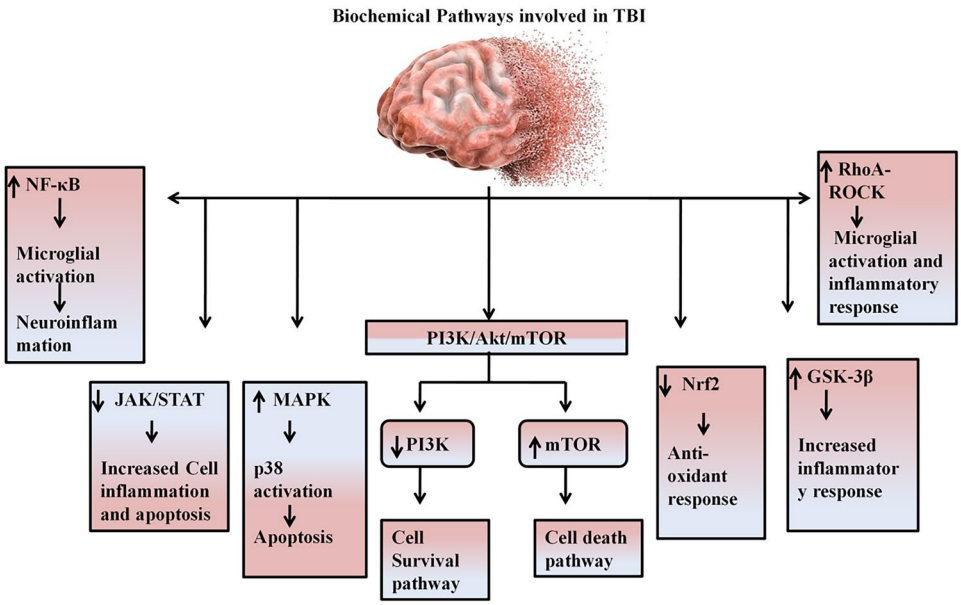

Fig. 2 Depiction of various biochemical pathways involved in traumatic brain injury: (**a**) nuclear factor-kappa B (NF-κB) signaling pathway, (**b**) Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, (**c**) mitogen-activated protein kinase (MAPK) pathway, (**d**) PI3K/Akt/mTOR signaling pathway, (**e**) GSK-3β signaling, (**f**) nuclear factor erythroid 2-related factor 2, (**g**) RhoA-ROCK signaling pathway

day were reported to ameliorate neuropsychiatric deficit (Talsky et al. 2010). Amantadine also improved concentration, attention, and alertness, and enhanced executive performance, with decreased agitation, aggression, fatigue, and anxiety (Nickels et al. 1999). Currently, amantadine is in a phase IV trial (NCT02321761).

Antioxidants

Brain damage due to post-traumatic oxidative stress may be reduced by the production of corresponding antioxidants, which scavenge free radicals. Numerous antioxidants have been shown to promote mitochondrial repair and decrease the mitochondrial decline in ATP biosynthesis after TBI (Bains and Hall 2012). *N*-acetylcysteine showed potential treatment effects in a TBI rat model, as it can cross the BBB and has antiapoptotic properties, and thereby improves neural cell survival. *N*-acetylcysteine increases brain glutathione and improves mitochondrial energetics (Xiong et al. 1999; Pandya et al. 2014). Methylprednisolone (a synthetic glucocorticoid) is a widely used drug to control central nervous system (CNS) edema due to its high anti-inflammatory potency. Methylprednisolone was shown to inhibit TNF-α expression and NF-kB activation after spinal cord injury in rats (Xu et al. 1998), and was evaluated in a clinical phase III trial (NCT00004759). Cutler et al. demonstrated the effect of progesterone in attenuating edema and secondary inflammation and improving short-term motor recovery and cell death after TBI (Cutler et al. 2007). Studies show that NIM811 and ciclosporin A (CsA) can reduce lipid peroxidation and protein nitration damage to mitochondria (Mbye et al. 2008). CsA has shown neuroprotective effects in immature models of focal and diffuse TBI. CsA preserved mitochondrial bioenergetics and significantly limited neuropathology by blocking mPTP (Kilbaugh et al. 2011). A phase II clinical study of CsA has also been completed (NCT01825044). Hydrogen-rich saline has a potential protective effect against TBI by reducing oxidative stress (Ji et al. 2012). A key endogenous antioxidant, coenzyme, proved effective in reducing neuronal injury and mitochondrial superoxide, enhancing mitochondrial electron transport, and restoring mitochondrial membrane potential. Coenzyme Q10 supplementation in TBI reduced secondary injury and was useful in reducing oxidative stress (Duberley et al. 2014). Sullivan et al. evaluated the effects of CsA in a mouse model of TBI, which revealed that CsA modulated mPTP and maintained mitochondrial homeostasis.

Anti-neuroinflammatory and Antiapoptotic Drugs

The neuroprotective effect of minocycline, a tetracycline derivative, was studied in an animal model of TBI. Minocycline was found to inhibit microglial activation and release pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α (Homsi et al. 2009). Protection against inflammation and apoptosis has been demonstrated by minocycline in various other experimental models of neurological diseases such as Alzheimer's disease and stroke (Kim and Suh 2009; Grewal et al. 2019). It reduced IL-1β levels by 50% in the cortex of a mouse model of closed head injury (CHI) by inhibiting microglial activation and improving

neurological outcome (Bye et al. 2007) (Fig. 2). Minocycline reduced cerebral edema and preserved BBB integrity by inhibiting matrix metalloproteinases (Bye et al. 2007; Homsi et al. 2009). Early administration of minocycline in a rat mild blast model was also shown to reduce inflammation and glial protein markers S100β and MCP-1. Improvements in anxiety, locomotion, and spatial memory were seen as well (Kovesdi et al. 2012). A phase II clinical study (NCT01058395) of minocycline has been completed, showing a therapeutic outcome in patients of reduced microglial and interleukin 1 beta (IL-1β) expression. In TBI, erythropoietin (EPO), a type 1 cytokine superfamily, and its receptor are extensively upregulated. The neuroprotective role of rhEPO in reducing neuronal apoptosis and inflammation was revealed in a rodent model of experimental CHI (Yatsiv et al. 2005). Zhou et al. also reported that EPO reduced neuroinflammation via downregulation of adhesion molecules, pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α, and the NF-κB inflammatory pathway, and reduced microglial activation. EPO also induces antiapoptotic effects by upregulating antiapoptotic proteins Bcl-X and phospho-Akt. Other useful EPO effects include enhanced neurogenesis, reduced NO production, and alleviation of brain swelling (Zhou et al. 2017).

Interestingly, in 2010, EPO was successfully used to treat patients with mild to severe TBI. Currently, EPO is under phase III clinical evaluation in TBI patients (NCT03061565). Another study by Zhang et al. suggested that resatorvid provided neuroprotection by reducing the protein levels of TAK1, p-TAK1, TNF-α, and IL-1β (Zhang et al. 2014). A synthetic peptide analog, NNZ-2566, has been demonstrated to be neuroprotective in a rat model of penetrating ballistic-like brain injury (PBBI), where it decreased the expression of numerous inflammatory mediators. NNZ-2566 has completed a phase II clinical trial (NCT01366820) (Table 1), and it showed improvement in cognitive and neuropsychological functioning of TBI patients.

Statins have also been shown to promote functional recovery following TBI in rodents by inhibiting caspase-3 activation and apoptotic cell death, and stimulating neurogenesis by enhancing the expression of several growth factors (Lu et al. 2004; Wu et al. 2008a, b). Clinical evaluation is still needed to validate the neuroprotective benefits of statin treatment after TBI. The effects of rosuvastatin on TBI-stimulated cytokine variation were evaluated in a phase I/II trial (NCT00990028) (Xiong et al. 2015). Progesterone also demonstrated helpful effects in animal models of TBI and clinical improvement in two phase II randomized controlled trials, but the study was terminated in phase III (NCT00822900) (Stein et al. 2015).

Neurorestoration Cell-Based Therapy for TBI Recovery

Neurovascular regeneration has been reported to have a substantial role in brain function recovery after injury (Xiong et al. 2010). In adults, neurogenesis has been reported in the hippocampus at the subgranular zone in the dentate gyrus (DG) and subventricular zone (Ehninger et al. 2008). It has been extensively reported in animal models that TBI helps induce neurogenesis in the cerebral cortex and dentate gyrus (Sun et al. 2009). A G-actin sequestering molecule called thymosin beta-4 (Tb4) in the cells, when injected in animals, increased the proliferation of neuronal precursor cells (NPCs). It also helps to enhance angiogenesis and promote NPC differentiation. TBI causes an increase in vascular density in the brain's cortex and is related to synaptogenesis and angiogenesis that may help in TBI recovery (Zhang et al. 2014). A recent study reported that Tb4 active peptide fragment and *N*-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) increased the number of dendritic spines in the rat's injured brain, thus improving neurogenesis and angiogenesis (Zhang et al. 2017). Stem cell therapy has emerged as a therapeutic avenue for CNS injuries and neurological disorders over the past few decades (Cao et al. 2002). Neural stem cell (NSC) transplantation in the brain through stereotactic injection is the commonly used delivery method. A study has also been conducted on embryonic stem cell (ESC) transplantation in TBI. It was reported that post-traumatic inflammatory response after TBI inhibits the survival and integration of transplanted ESCs (Molcanyi 2007). ESC transplantation has been shown to improve neurological outcomes but is associated with a risk of tumorigenesis (Forraz et al. 2013; Rao 2007). Many studies have proven the comprehensive benefits of stem cells for treating spinal cord and brain injuries (Taguchi et al. 2015). Different types of cells have been used for TBI recovery. Transplantation of mesenchymal stem cells (MSCs) for TBI recovery has been evaluated in animal models. MSCs were obtained from the umbilical cord, adipose tissue, and bone marrow (Hu et al. 2019; Wang et al. 2015). Transplantation of MSC should occur within 24 h after TBI. MSCs have been shown to release various growth factors including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), vascular endothelial growth factor (VEGF), and fibroblast growth factor 2 (FGF-2) that can improve neurological outcome after TBI (Wu et al. 2008a, b; Sun et al. 2009). Currently, a phase II clinical study on the use of chloroxylenol NGF in TBI patients has been completed (NCT01212679). Chloroxylenol upregulates neurogenesis-associated protein. NSC or NPC proliferation has recently

Table 1 Drugs in clinical phase for TBI treatment

Drug	Study	Mechanism	Status	NCT identifier number
Ciclosporin A (obtained from fungus *Tolypocladium inflatum*)	Copenhagen Head Injury Ciclosporin (CHIC) Study	Ciclosporin A inhibits the opening of the mitochondrial permeability transition pore and apoptosis	Phase II completed	NCT01825044
Minocycline	Safety and Feasibility of Minocycline in the Treatment of Traumatic Brain Injury (TBI)	Reduces microglial activation and interleukin 1 beta expression	Ongoing phase 1/II	NCT01058395
Dexanabinol	Dexanabinol in Severe Traumatic Brain Injury	Dexanabinol may prevent some of the adverse effects of glutamate on the brain and may protect the brain against uncontrollable swelling and death	Phase III completed	NCT00129857
Methylprednisolone	Methylprednisolone Given by 24 h or 48-h Infusion Versus Tirilazad for Acute Spinal Cord Injury	Inhibits TNF-α expression and NF-kB activation	Phase III completed	NCT00004759
Rosuvastatin	Effect of Rosuvastatin on Cytokines After Traumatic Brain Injury	Alters the immunological response after head injury by modulating TNF-alpha, IL-6, IL-1	Phase II completed	NCT00990028
Progesterone	Progesterone for the Treatment of Traumatic Brain Injury III (ProTECT)	Progesterone infusion results in reduced neuronal loss, enhanced remyelination, improved functional recovery, and reduced cerebral edema	Terminated at Phase III	NCT00822900
Amantadine	Effect of Amantadine Administration on Spatial Functioning Following Traumatic Brain Injury	Stimulates dopamine receptor that may help to recover the nervous system after traumatic brain injury	Phase IV	NCT02321761
NNZ-2566	A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study of NNZ-2566 in Patients with Traumatic Brain Injury	Protects against penetrating ballistic-like brain injury (PBBI)-induced inflammation and apoptosis and promotes functional recovery	Phase II	NCT01366820
Erythropoietin	Long Term Effects of Erythropoietin in Patients With Moderate to Severe Traumatic brain injury	Exerts antiapoptotic, anti-inflammatory, and antiedematous effects by activation of JAK/STAT pathway	Phase III	NCT03061565
Chloroxylenol	Chloroxylenol Completed Phase 2 Trials for Traumatic Brain Injury (TBI) Treatment	Upregulates neurogenesis-associated protein doublecortin (DCX), sustaining neuronal growth, differentiation, and survival of brain cells	Phase II	NCT01212679

been shown to enhance post-TBI functional recovery and stabilize the cortical microenvironment (Patel 2016; Gritti et al. 2002). Treatments that use NSC transplantation showed hippocampal neurogenesis and neuroprotection, with improved functional results (Balaya et al. 2015). Cell transplantation ranges from 0.15 to 25 million cells per kilogram of body weight per animal model (Gennai et al. 2015). Cell-derived exosome therapy is another approach for treating post-TBI-mediated neural injury. Exosomes are tiny vesicles that carry proteins, mRNA, miRNA, and lipids from their donor cells and support intracellular communication. Exosomes interact with brain parenchyma cells and aid in brain remodeling and neurogenesis (Ghosh et al. 2020). Arien-Zakay et al. (2014) also demonstrated the neurotherapeutic effect of transplanted CD45+ hematopoietic cells derived from human umbilical cord blood (HUCB) in mice after TBI. Pretreatment of the cells with anti-human-CD45 antibody reduced the lesion volume in the mice (Arien-Zakay et al. 2014). The analysis of cytokine levels in the extracts of TBI brain cortices of mice has revealed acute immunomodulatory effects due to xenotransplanted HUCB CD45+ cells that provide further insights into the CD45 marker as a predictor of HUCB unit quality for neurotherapy in TBI (Gincberg et al. 2018).

Approaches for Therapeutic Targets in Traumatic Brain Injury

Significant research has led to expanded knowledge about the pathophysiology and molecular mechanism behind TBI. Primary injuries in TBI cannot be reversed, whereas secondary damage that develops over months to years is responsive to therapeutic interventions. Due to the extended injury period, which consists of excitotoxicity, neuroinflammation, oxidative stress, apoptotic cell death, axonal degeneration, and neuroinflammation, for treatment to be effective, efficient therapeutic agents are needed over a subacute or chronic period.

Nuclear Factor-kappa B (NF-κB)

The nuclear factor kappa B (NF-κB) signaling pathway is an inflammatory signaling pathway because it synthesizes pro-inflammatory genes and inflammatory molecules such as chemokines and cytokines (Liu et al. 2017). Several papers have confirmed the role of NF-κB as a downstream element for the activation of specific receptors, including tumor necrosis factor receptor-associated factor 6 (TRAF6) and Toll-like receptor 4 (TLR4), in animals and humans suffering from TBI; therefore, targeting of NF-κB may decrease inflammation and apoptosis after TBI (Carmody and Chen 2007). Experimental studies report the activation of NF-κB in neurons and glial cells in association with neuropathological disorders and neuroprotective activity (Singh and Singh 2020). A study also explored the role of CB1 receptors in mediating 2-AG neuroprotection after CHI in mice via CB1 receptor-mediated mechanisms that involve inhibition of intracellular inflammatory signaling pathways. (Panikashvili et al. 2005). NF-κB activation promotes inflammation in glial cells, whereas in neurons, NF-κB is involved in synaptic plasticity, neuronal development, and survival (Mattson and Camandola 2001). Increased levels of NF-κB were reported in rats after controlled cortical impact and fluid percussion brain injury as well as in biopsies of human contused brain tissue (McKeating and Andrews 1998; Yang et al. 1995).

Further, researchers have reported NF-κB activation due to cortical aspiration lesions in neurons of the degenerating cortex and astrocytes of the corpus callosum of the immature rat brain (Sanz et al. 2002). Trauma due to controlled cortical impact destroyed the BBB and increased brain injury volumes in transgenic mice due to elevated NF-κB activity in the brain (Sullivan et al. 1999a, b). A p50 subunit of NF-κB is present in neurons and is involved in neuronal survival from hippocampal injury, thus playing a crucial role in regulating repair and regeneration (Pennypacker et al. 2001). Chang et al. demonstrated that nanocurcumin induced neuroprotective effects against TBI via upward regulation of NF-κB (p65) and decreased mitochondrion-related caspase-9a expression (Chang et al. 2015). Thus these studies illustrate that NF-κB signaling has both beneficial and detrimental roles based on its expression on different cell types. Recent experimental studies have evaluated the expression of NF-κB in a mouse model of TBI, and treatment with metformin inhibited microglia activation-mediated inflammation via the NF-κB and MAPK signaling pathways (Tao et al. 2018). In a mouse model of TBI, dexmedetomidine attenuated increased expression of NF-κB and NLRP3 inflammasome (Zheng et al. 2018). Another study involving in vivo and in vitro TBI models showed increased expression of pro-inflammatory cytokines, IL-6 and IL-1β, tumor necrosis factor-α (TNF-α), and NF-κB. Treatment with a natural coumarin derivative, osthol, produced a significant reduction in inflammatory mediators and improved neurological function, increasing the number of neurons beside the injured site. Additionally, osthol treatment reduced the expression of all inflammatory mediators (Kong et al. 2019). Thus, NF-κB activation plays a pathophysiological role in TBI.

Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) Pathway

JAK-STAT is a critical pathway for the transduction of growth factors and cytokines involved in numerous biological processes including cell differentiation, cell proliferation, axon regeneration, inflammation, and apoptosis (Oliva et al. 2012). JAK-STAT pathway activation begins with binding a specific ligand to the cell surface receptor, followed by intracellular transduction triggered by JAK kinase recruitment. JAK initiates transcription and dimerization of STAT factors; other STAT translocates into the nucleus and binds to a specific DNA site for gene expression regulation. The inflammatory response after TBI reduces the expression of JAK/STAT which causes increased cell apoptosis in the cortical pericontusional zone (Oliva et al. 2012) (Fig. 2). Zhao et al. found that partial inhibition of JAK2 and STAT3 phosphorylation due to the administration of the JAK2 inhibitor AG490 resulted in worse neurological recovery after TBI. However, administration of recombinant erythropoietin (rhEPO) after a TBI enhanced the phosphorylation of JAK2 and STAT3 and decreased apoptosis of peri-injured cortex cells of rats. Administration of JAK2 inhibitor AG490 resulted in reduced pJAK2 and pSTAT3 and increased mRNA levels of several apoptosis-related genes, thereby suggesting that JAK2-STAT3 pathway activation is beneficial after TBI (Zhao et al. 2011).

Mitogen-Activated Protein Kinase (MAPK) Pathway

MAPKs are a threonine/serine-based protein kinase that plays a crucial role in signal transduction for cell proliferation, differentiation, and survival on its activation via phosphorylation in response to various cell injuries (Strniskova et al. 2002). Cascades are composed of p38, extracellular signal-regulated protein kinase (ERK), and c-Jun NH (2)-terminal kinase (JNK) pathways. Several studies have demonstrated that JNK and p38 cascade activation promotes neuronal injury along with cerebral ischemia and spinal cord injury (Otani et al. 2002). An in vitro model demonstrated rapid activation of ERK and astroglial proliferation following TBI (Carbonell and Mandell 2003). Abnormalities in the MAPK signaling pathway are found in the pathophysiology of TBI, and studies have shown that inhibiting this pathway is associated with enhanced cell survival in vitro and resulted in a considerable decrease in the volume of cortical lesions after 7 days. Otani et al. demonstrated the role of inhibition of ERK phosphorylation using MAPK/ERK (MEK) inhibitor U0126 and revealed that U0126 improved motor function post-TBI (Chi et al. 2013). JNKs are stress-activated protein kinases associated with neurodegeneration and are located in the nucleus of neuronal cells. TBI can result in JNK activation and the formation of a complex in the mitochondria of brain cells, leading to cell death (Dietrich and Bramlett 2016). During oxidative stress-induced damage, p38 kinase creates a proapoptotic effect in different TBI models that leads to inconsistent MAPK activation. Therefore, MAPK kinase activation does not have a defensive role in TBI.

PI3K/Akt/mTOR Signaling Pathway

The PI3K/Akt/mTOR signaling pathway is a major controller in neuronal cell growth, an outgrowth of the axon, and dendrite during the brain development process (Kumar et al. 2005). The activation of PI3K and downstream Akt is stimulated by various growth factors and hormones that regulate the mammalian target of rapamycin (mTOR) complex and target molecules such as mTORC1 and mTORC2 (Dibble and Cantley 2015). The function of mTOR is to integrate input from multiple upstream signals for cell apoptosis, inhibition of cell proliferation, and autophagy. Neuronal mTOR controls the production of proteins in cell bodies and axons that are crucial for cellular growth (Abe 2010). A study demonstrated the neuroprotective effect of rapamycin on outcomes in mice after brain injury. Rapamycin was shown to inhibit mTOR and reduce microglia/macrophage activation, increasing neuron survival (Erlich et al. 2007). This pathway has shown a debatable role, as a study revealed that PI3K activation and mTORC1 suppression by the mTORC1-specific inhibitor rapamycin after TBI presented beneficial effects on recovery as evaluated by the degree of tissue damage, progress in motor function, neurological score, and tasks related to learning and memory (Nikolaeva et al. 2016). Inhibition of the mTOR pathway in TBI mainly controls TBI-related symptoms such as epilepsy and inflammatory responses (Guo et al. 2013). TBI is associated with numerous abnormalities such as an increase in cellular, molecular and synaptic activity in the brain, and mTOR further improves protein synthesis and synaptic plasticity that might cause an abnormal rise in excited electrical signals, thereby contributing to epileptogenesis in the injured brain (Guo et al. 2013). Rapamycin has been used extensively to suppress the activation of mTORC1 in animal models subjected to cortical malformations and prolong survival by suppressing neuronal abnormalities, glial pathology, and intense seizures (Sadowski et al. 2015). Various drugs have been shown to activate the Akt/mTOR/PI3K pathway. Stachydrine showed a beneficial effect on neurodegeneration induced due to TBI by increasing the expression of the PI3K/Akt/mTOR pathway in a rat model of TBI (Yu et al. 2018). Propofol is another drug that reduced brain injury

induced by subarachnoid hemorrhage in rats due to the PI3K/Akt pathway (Zhang et al. 2019).

Bisperoxovanadium was also shown to mediate neuronal protection via activation of PI3K/AKT-mTOR signaling after traumatic spinal injury in rats (Walker et al. 2019). Dexmedetomidine recently showed a neuroprotective effect in rats suffering from TBI via the PI3K/Akt/mTOR signaling pathway (Shen et al. 2017). In another study, post-conditioning with sevoflurane attenuated neuronal apoptosis induced due to TBI by promoting autophagy via the PI3K/AKT signaling pathway (He et al. 2018). Sodium hydrosulfide (NaHS) restored mitochondrial function, which improved functional recovery after TBI in rats. Additionally, it inhibited autophagy by activating the PI3K/Akt/mTOR signaling pathway (Xu et al. 2018a, b, c). Thus, the PI3K/Akt pathway has a beneficial role in neurodegeneration induced by TBI.

GSK-3β

Glycogen synthase kinase 3 (GSK-3) β is known for regulating glycogen metabolism, protein synthesis, microtubule dynamics, cell differentiation, cell death, and apoptosis. GSK-3β signaling is responsible for neuronal death triggered by numerous toxic stimuli such as amyloid-beta or apoptotic proteins such as p53 (Forde and Dale 2007). The two major signaling pathways, also are known as protein kinase B, that regulate GSK-3β activity are Wnt and Akt (Fang et al. 2000). Phosphorylation of GSK-3β results in pro- and anti-inflammatory responses in monocytes due to Akt activation. Depending upon the role of GSK-3β in apoptosis, selective small GSK-3β inhibitors protect cells from these proapoptotic stimuli. Abnormal activation of GSK-3β is linked with neurodegeneration and chronic neuroinflammation (Llorens-Marítin et al. 2014; Li et al. 2014). Numerous studies have demonstrated the role of GSK-3β in neuroinflammation in TBI models and revealed the beneficial role of various GSK-3β inhibitors in TBI. Dash et al. showed increased expression of GSK-3β in rats induced with controlled cortical impact and evaluated the effect of lithium as a GSK-3β inhibitor. The results showed that lithium inhibited GSK-3β-induced oxidative stress, apoptosis, and mitochondrial and endoplasmic dysfunction by increasing the phosphorylation of GSK-3 via activation of Akt (Dash et al. 2011). Another study by Jiang et al. revealed the neuroprotective effect of breviscapine on TBI in rats, associated with inhibition of the GSK3β signaling pathway. Recently, Farr et al. (2019) demonstrated that an antisense GSK-3β (GAO) gene targeted GSK3β in a mouse model of closed-head concussive TBI (Jiang et al. 2017). The mice subjected to TBI were injected with GAO or random antisense (RAO) 15 min post-injury, which led to increased GSK-3β inhibition after TBI with antisense directed at GSK-3β and improved learning and memory. Therefore, GSK-3β inhibition with various GSK-3β inhibitors has demonstrated a beneficial role in TBI, repurposed in a clinical study.

Nuclear Factor Erythroid 2-Related Factor 2

Nuclear factor erythroid 2-related factor (Nrf2) is a gene transcription factor that plays a defensive role in cells against various harmful stimuli. The site of Nrf2 is mainly in the cytoplasm bound to its inhibitor Kelch-like ECH-associated protein 1 (Keap1) that prevents the nuclear entry of Nrf2 (Suzuki and Yamamoto 2017). During stress conditions or other types of stimulus such as tert-butylhydroquinone (tBHQ), Nrf2 dissociates from Keap1 to translocate in the nucleus and bind to the ARE, and stimulates the transcription of genes encoding protective factors (Kraft et al. 2004). In in vivo cerebral ischemia, Nrf2-regulated genes have shown a neuroprotective effect, whereas Nrf2-knockout mice are more responsive to ischemia/reperfusion-induced brain injury and intracerebral hemorrhage (Shih et al. 2005). In the TBI model, neuroinflammation, oxidative stress, and neurodegeneration have previously been reported (Fig. 2). Studies have shown the protective role of Nrf2 in the TBI model, such as Nrf2 activity inducer; sulforaphane has also been reported to reduce brain edema after TBI (Zhao et al. 2005). Xu et al. reported that luteolin lowered the levels of intracellular reactive oxygen species (ROS) and improved neuron survival via the Nrf2-ARE pathway. Recent studies have shown that Nrf2 downregulation leads to increased oxidative stress, TGF-β1, NF-kB, and MMP3/9, promoting neuronal apoptosis and neuroinflammation. A study exploring the regulatory role of Nrf2 in Nrf2+/+ and Nrf2−/− mice that received 15 psi fluid percussion injury revealed that Nrf2−/− mice had worse brain injury (increased pro-inflammatory cytokines, markers of oxidative stress, and apoptosis) even after 24 h following trauma (Bhowmick et al. 2019). Zhang et al. also evaluated the protective effect of sodium aescinate (SA), a natural plant extract, in both in vivo and in vitro TBI mouse models, and SA was shown to suppress TBI-induced oxidative stress, neuron cell death, and apoptosis via activation of the Nrf2 pathway (Zhang et al. 2020). Dong et al. evaluated the effect of curcumin treatment in wild-type (WT) and Nrf2-knockout (Nrf2-KO) mice to investigate the role of Nrf2 signaling in the TBI model. The results showed that wild-type mice treated with curcumin had decreased microglia activation, neutrophil infiltration, and apoptosis in the injured ipsilateral cortex. However, deletion of Nrf2 diminished the neuroprotective effects of curcumin in Nrf2-KO mice after TBI. Thus Nrf2 upregulation plays a protective role in TBI, and its downregulation yields the opposite effect.

Rho-GTPase

Members of the Rho-GTPase family (RhoA, Cdc42, and Rac1) are the primary controller of cell adhesion and cytoskeletal dynamics, regulating a broad range of cellular functions (Chi et al. 2013). Recent studies have shown that Rho GTPase signaling dysregulation may be implicated in the pathogenesis of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) (Mulherkar and Tolias 2020). RhoA has been reported to inhibit axonal regeneration along with apoptotic responses after TBI, as continuous upregulation of active RhoA impairs axonal regeneration and neuritis repair. CNS injury often leads to astrocyte activation and proliferation (Mulherkar and Tolias 2020). The association of astrocytes with oligodendrocytes, microglia fibroblasts, and meningeal cells steadily develops into a scar-like structure, which inhibits axonal regeneration and impedes TBI recovery. RhoA activation has been reported in the ipsilateral cortex of rats with induced lateral fluid percussion injury (FPI) (Dubreuil et al. 2006). Likewise, increased RhoA activity was observed in the glial cells and spinal cord of mice and a rat model of spinal cord injury (SCI) (Wu and Xu 2016). Currently, a small inhibitor of GTPase RhoA has emerged to play an influential role in axonal regeneration. Exoenzyme C3 transferase is an enzyme found in *Clostridium botulinum* that blocks the downstream signaling responsible for inhibition of axonal regeneration via inhibition of ADP-ribosylate Rho proteins by transferring the ADP-ribose moiety from NAD to the acceptor amino acid residue asparagine-41 of the Rho proteins (Aktories and Just 2004). The effect of C3 transferase in promoting axonal regeneration has been studied in both in vitro and in vivo animal models of SCI and peripheral nerve injury (Kubo et al. 2007; Forgione and Fehlings 2014). SCI-induced rats treated with the C3 peptide showed improvement in neurological outcomes (Zhao et al. 2019). Another C3 derivative, BA-210, was also demonstrated to enhance functional regeneration in animal models of spine injuries (Lord-Fontaine et al. 2008). Thus, inhibition of RhoA signaling in TBI can be an effective approach for axonal regeneration.

Novel Therapeutic Targets for TBI

IRE1/XBP1/ RACK1 Signaling

Receptor for activated protein kinase C 1 (RACK1) is a protein complex bearing seven WD40 domains, and is also recognized as guanine nucleotide-binding protein subunit beta-2-like 1 (Liliental and Chang 1998). A recent study showed that RACK1 stimulates inositol-requiring enzyme 1 (IRE1) signaling after binding to it, where IRE1 is a stress sensor from the proximal endoplasmic reticulum. In the CNS, RACK1 protects neurons by regulating various cell survival signaling events (Ma et al. 2014). Activated IRE1 undergoes unusual mRNA splicing that encodes transcription factor X-box binding protein-1 (XBP1) and regulates the expression of glucose-regulated protein 78 (GRP78). Evidence has shown that IRE1-XBP1 signaling protects neurons from apoptosis in CNS diseases. For example, overexpression of XBP1 prevented amyloid-β-induced neurotoxicity in cultured neurons (Casas-Tinto et al. 2011), and removal of XBP1 caused deterioration of dopaminergic neurons in a Parkinson's mouse model (Valdés et al. 2014). Ni et al. recently evaluated the effects of an in vivo RACK1 knockdown TBI rat model and RACK1-overexpressed TBI rat models. The results showed increased neuronal apoptosis, BBB disruption, brain edema, and neurological deficits, whereas RACK1 overexpression in the TBI rat models induced protective effects. Furthermore, IRE1 inhibitor 3,5-dibromosalicylaldehyde (DBSA) administration reversed the protective effects of RACK1 overexpression against brain injury and decreased p-IRE1, XBP1, and GRP78 expression (Ni et al. 2018). Thus IRE1/XBP1/ RACK1 signaling can be an effective approach for protecting neurons from apoptosis in TBI.

TGF-β1 Signaling

TGF-β signaling is a distinct indicator of microglial inactivation. Prior studies have revealed the protective role of TGF-β1 in CNS disorders. A study by Taylor et al. showed that TGF-β1 promoted functional recovery after intracerebral hemorrhage by modulating the alternative activation of microglial cells (Taylor et al. 2017). Another study showed that TGF-β1 signaling provided persistent anti-inflammatory activity in rats induced with middle cerebral artery occlusion (Islam et al. 2018). TGF-β1 signaling also prevented dopaminergic neuronal loss with reduced pro-inflammatory cytokines (Chen et al. 2017). However, the effects of TGF-β1-mediated microglial activation on axonal injury after TBI had not been reported until a recent study by Zhao et al. TBI rat models showed reduced expression of TGF-β1 after TBI and increased expression of inflammatory cytokines, but TGF-β1 treatment inhibited neuroinflammation and microglial/macrophage proliferation (Zhao et al. 2020). This protective effect of TGF-β1 was reversed by LY2109761, and proved that TGFβ1 tends to play a defensive role in axonal injury and may be an effective target for treating the early stages of TBI.

NLRP3

Nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) is a multi-protein complex that, upon sensing dangerous stimuli, assembles and triggers the activation of caspase-1 and promotes expulsion of the pro-inflammatory cytokines IL-18 and IL-1β (Lamkanfi et al. 2011). These cytokines activate the immune system following TBI, leading to neuroinflammation. Cell death via apoptosis and proapoptotic pathways is mediated by caspase-1 activation (Mortezaee et al. 2018). NLRP3 contains three proteins, i.e. sensor protein, apoptosis-associated speck-like protein holding caspase recruitment domain (ASC), and pro-caspase 1 as the precursor enzyme (Mortezaee et al. 2018). In an animal model of TBI, NLRP3 inflammasome blockage showed beneficial effects by decreasing neuroinflammation. Ismael et al. revealed that selective inhibitor of NLRP3 inflammasome (MCC950) attenuated proapoptotic and pro-inflammatory signals during the acute phase of TBI (Ismael et al. 2018). Xu et al. recently evaluated the MCC950 effect on a mouse model of TBI against leukocyte infiltration, microglia activation, disruption of the BBB, and long-term neurological defects; the results revealed that MCC950 treatment improved neurological function after TBI by reducing brain edema and lesion volume, and improving both motor and cognitive function (Xu et al. 2018a, b, c). Zheng et al. also revealed that dexmedetomidine inhibited NLRP3 inflammasome and microglial cell activity in the hippocampus of a TBI rat model (Zheng et al. 2018). Thus the NLPR3 inflammasome is associated with an inflammatory response in TBI and is a promising therapeutic target for TBI patients.

TRPM7

TRPM7 is a melastatin-related subfamily of TRP channels that comprises eight elements, denoted as TRPM1–8 (Inou et al. 2005). Expression of TRPM members occurs in all tissues and in neuronal cells. TRPM7 activation has a direct role in Ca^{2+}-mediated neuronal death. Recently, however, it has been reported that there is also a non-excitotoxic mechanism involved in cell death. For example, TRPM7 channels promoted neuronal death once activated in neurons cultured in hypoxic conditions, and therefore its suppression showed resistance to ischemic death of neurons in transient global cerebral ischemia models (Aarts and Tymianski 2005). Li et al. revealed that carvacrol, an inhibitor of TRPM7, attenuated neuronal injury due to trauma by inhibiting the entry of Ca^{2+} into the neuronal cell and regulating Ca^{2+} homeostasis (Li et al. 2014). However, the exact function of TRPM7 in neuronal injury after TBI had not been determined. Therefore, Xu et al. investigated the role of TRPM7 in the cerebral cortex of rats with TBI and found that TRPM7 activation increased lipid peroxidation, brain edema, and neuronal apoptosis. Also, treatment with shRNA injected with viral vectors via an intracortical route inhibited TRPM7 and reversed the effect caused by TRPM7. The mechanism of protection aided by TRPM7 inhibition was due to augmented phosphorylation of endothelial nitric oxide synthase (eNOS) and Akt.

Further, a specific inhibitor, LY294002, moderately abolished the beneficial effects of TRPM7 inhibition and its antioxidant effects. Thus these results confirmed that TRPM7 inhibition in the cerebral cortex exerted neuroprotective effects in TBI via Akt/eNOS pathway activation. TRPM7 therefore represents a promising target in drug development for TBI treatment (Xu et al. 2018a, b, c).

Future Perspective

TBI has become a serious health and socioeconomic problem throughout the world, imposing a tremendous healthcare burden on modern society and the need for effective therapy. The current neuroprotective method involves approaches that stimulate inhibition of neuronal cell death mechanisms and recovery or normal functioning of non-neuronal cells. Numerous treatments have been developed to date including neurorestorative, anti-inflammatory, and neuroprotective agents. Still, a direct consequence of TBI is related to the integrity of the BBB, while dysfunction of BBB after TBI contributes to secondary damage. Only peptides and therapeutic proteins through the intranasal route cross the endothelial tight junctions and reach the injury site. In an animal model of TBI, direct delivery of a therapeutic agent to the CSF is feasible via an intraventricular route, whereas surgical intervention is often required in clinical management to relieve intracranial pressure and edema to enable direct drug delivery. Therefore, developing an effective drug delivery system may allow sustained and controlled release of therapeutic agents that will promote recovery from secondary brain damage after TBI. One such delivery system is osmotic mini-pumps tested in experimental models for successful delivery of NGF and S100B neurotrophic protein at a constant rate into the lateral ventricles in the brain, which have been shown to promote cognitive function (Kleindienst et al. 2004). Another promising drug delivery system is drug encapsulation in nano- and microparticles that allow controlled and sustained drug delivery, but their use in TBI treatment is limited. One of the most popular synthetic biopolymers used as nanocarriers for drug delivery purposes is the family of polylactic acid (PLA) and polyglycolic acid (PGA) (Soppimath et al. 2001). Exosomes, lipid bilayer membrane vesicles, have gained attention in promoting functional recovery in

animal models of TBI. They can carry therapeutic molecules ranging from mRNAs, microRNAs, and proteins to lipids. Intravenous administration of macrophage exosomes pre-loaded with BDNF has been shown to successfully deliver the protein to the brain (Yuan et al. 2017). Neuroprotective strategies for the management of TBI target specific mechanisms involved in the complex secondary-injury cascade. Altering the post-injury cellular events has historically been the primary neuroprotective strategy. Recent neuroprotection methods are based on therapeutic approaches that initiate neuronal recovery with optimal function by inhibiting the principle cell death mechanism. Targeting specific molecular mechanisms for TBI management and post-injury care is essential. There is a vital need for the advancement of novel treatment to help limit the impact of TBI. Many target-based therapies have been proposed that have not yet been considered for clinical evaluation. More focus should be given to developing goal-based treatment to effectively manage or treat TBI.

Conclusion

The lack of efficient treatments and the appearance of disabilities in a number of TBI survivors have led to continuous research efforts over the past few decades toward developing a novel therapeutic strategy. The current review has broadly discussed the pathophysiological mechanism of TBI, pharmacological treatment approaches, and various biochemical pathways involved in brain injury. Novel targets in the pathophysiology of TBI have also been discussed that could open a potential avenue for TBI treatment.

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Declarations

Consent for Publication All authors have read and given their consent for the final manuscript to be published.

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