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REVIEW

The protective effects of statins in traumatic brain injury

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Abstract

Traumatic brain injury (TBI), often referred to as the "silent epidemic", is the most common cause of mortality and morbidity worldwide among all trauma-related injuries. It is associated with considerable personal, medical, and economic consequences. Although remarkable advances in therapeutic approaches have been made, current treatments and clinical management for TBI recovery still remain to be improved. One of the factors that may contribute to this gap is that existing therapies target only a single event or pathology. However, brain injury after TBI involves various pathological mechanisms, including inflammation, oxidative stress, blood-brain barrier (BBB) disruption, ionic disturbance, excitotoxicity, mitochondrial dysfunction, neuronal necrosis, and apoptosis. Statins have several beneficial pleiotropic effects (anti-excitotoxicity, anti-inflammatory, anti-oxidant, anti-thrombotic, immunomodulatory activity, endothelial and vasoactive properties) in addition to promoting angiogenesis, neurogenesis, and synaptogenesis in TBI. Supposedly, using agents such as statins that target numerous and diverse pathological mechanisms, may be more effective than a single-target approach in TBI management. The current review was undertaken to investigate and summarize the protective mechanisms of statins against TBI. The limitations of conducted studies and directions for future research on this potential therapeutic application of statins are also discussed.

Keywords Statins · Brain · Trauma · Pleiotropic effect · Neuroprotection

Abbreviations

AD	Alzheimer's disease
AJs	Adherens junctions
ATP	Adenosine 5 triphosphate
BBB	Blood-brain barrier
$Ca^{2}+$	Calcium
CDC	Center for disease control and prevention
CNS	Central nervous system
CRP	C-reactive protein
DAMPs	Damage-associated molecular patterns
DB RCT	Double-blind randomized clinical trial
DCs	Dendritic cells
DG	Dentate gyrus
DRS	Disability rating scale
eNOS	Endothelial isoform of nitric oxide synthase
EPCs	Endothelial progenitor cells
ESR	Erythrocyte sedimentation rate
FDA	Food and drug administration
GCS	Glasgow coma scale
GOS	Glasgow outcome scale
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme A
ICAM-1	Intercellular adhesion molecule 1
ICP	Intracranial pressure
ICU	Intensive care unit
IL	Interleukin
iNOS	Inducible isoform of nitric oxide synthase
LDL	Low-density lipoprotein
LTP	Long-term potentiation
MRS	Modified rankin scale

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MSCs	Mesenchymal stromal cells
NMDA	N-methyl-D-aspartate
nNOS	Neuronal isoform of nitric oxide synthase
NO	Nitric oxide
NSC	Neural stem cells
PMN	Polymorphonuclear leukocytes
PRRs	Pattern recognition receptors
ROS	Reactive oxygen species
TBI	Traumatic brain injury
TJs	Tight junctions
TLR	Toll-like receptors
TNF-α	Ttumor necrosis factor-alpha
Tregs	Regulatory T cells
VEGF	Vascular endothelial growth factor
VEGFR-2	VEGF receptor
vWF	von Willebrand factor

Introduction

Traumatic brain injury (TBI), in healthcare referred to as the "silent epidemic" [1], is the leading cause among all trauma-related injuries globally of mortality and morbidity, with considerable medical, familial, social, and economic consequences [2, 3]. It affects approximately 69 million people worldwide each year [4]. According to data from the Centers for Disease Control and Prevention (CDC), nearly 2.8 million people in the United States of America (USA) sustain a TBI, with almost 56,000 TBI-related deaths annually [5], and an estimated 5.3 million individuals living with TBI-related dysfunction [6, 7]. TBI can cause both primary and secondary neuronal tissue damage, leading to complex pathogenesis that results in transient or permanent neurological deficits [8] or neurological complications, such as Alzheimer's disease (AD), impaired attention, mental health issues, poor executive function, and seizures, are common outcomes of TBI [9].

Although therapeutic approaches for TBI have been remarkably improved in recent years, there remains a lack of effective treatments and clinical management [10]. Novel treatment strategies being explored include neuro-repair methods, infusion of mesenchymal stromal cells (MSCs), remote ischemic conditioning, and medication such as sex hormones, melatonin, minocycline, and hyperoxia [11, 12]. Although these interventions have been successful in laboratory studies and preclinical models, clinical trials have generally failed to show true benefits in humans [13]. While statins are among the most widely used class of lipid-lowering therapies used either alone or in combination with other agents [14–17], they also exert lipid-independent effects [18–26]. These medications have exhibited the most promise in improving the outcomes of TBI patients [12, 27, 28]. The Operation Brain Trauma Therapy Consortium also recommends statins for brain damage as a possible pharmacotherapy for TBI and its sequelae [29, 30]. However, limited and inconsistent data regarding statin efficacy in TBI exist in the literature. This may be attributed to the heterogeneity of TBI pathology, the variety of statins studied, differing analytical methodologies across studies, heterogeneous populations, inclusion of those with pre-existing cognitive impairments, and differing endpoints. The current review was undertaken to delve into the immune system alterations that underlie TBI pathogenesis and to explore the mechanisms through which statins may limit TBI severity. We will also highlight the gaps in the extant evidence on the therapeutic potential of statins in TBI.

Pathophysiology of TBI

Hypoxic conditions in the post-TBI brain cause the underproduction of adenosine 5 triphosphate (ATP), which impairs ionic homeostasis and leads to intracellular sodium overload and intracellular hypercalcemia [31]. Glutamate released from neuronal death, and its overproduction, results in increased extracellular glutamate concentrations contributing to excitotoxic effects [32]. Astrocytes absorb glutamate and transform it into glutamine as an alternative energy source in normal conditions. However, in this pathologic condition, astrocytes cannot sufficiently remove excessive glutamate from the extracellular space. Glutamate stimulates neuronal receptors, such as N-methyl-D-aspartate (NMDA), inducing an influx of abundant calcium ($Ca^{2}+$) and sodium. This ion imbalance leads to cell membrane depolarization and elevated intracellular $Ca^{2}+$ levels, resulting in mitochondrial dysfunction, diminished ATP production, energy failure, and cell apoptosis. Production of reactive oxygen species (ROS) and nitric oxide (NO) species occurs following the loss of mitochondrial integrity. These cumulatively induce oxidative stress, negatively impacting membrane lipids, proteins, and DNA. Additionally, free Ca2 + activates various enzymes, e.g. caspases, which relate to DNA fragmentation and cell death [33, 34]. Further calcium-activated enzymes, for example, calpains impair axonal function and transport by disrupting the axon's cytoskeletal filaments [35]. Primary injury causes glial cell (microglia and astrocyte) activation, resulting in the production of Damage-associated molecular patterns (DAMPs), and triggering inflammatory responses in the brain [36, 37]. Microglia are activated when they detect DAMPs, and then they can clear debris and generate neurotrophic agents, cytokines, and ROS. As a result, immune cells such as neutrophils and monocytes migrate to this inflammatory microenvironment. This leads to further ROS

production, generation of excitatory neurotransmitters, and additional cellular migration of monocytes and neutrophils to the injured area. Recruited neutrophils and monocytes display a desirable mechanism to eliminate pathological debris and repair, although they may also exacerbate inflammation and precipitate neuronal defects [38]. They diminish BBB integrity, leading to increased extracellular fluid that, combined with cell swelling, results in brain edema and elevated intracranial pressure (ICP) [34]. Necrotic neurons release HMGB-1 as a DAMP, causing microglia to produce interleukins (IL) e.g. IL-6; which induces astrocytes to express the water channel aquaporin4, leading to cytotoxic swelling. The multifactor-driven edema raises ICP, decreases cerebral perfusion pressure, and blood flow, and establishes an aggressive cycle that intensifies the hypoxic environment and disrupts the brain's ATP/energy supply. As a result of these variations, further injury to grey and white matter and a continuous discount in synaptic plasticity often occur [38]. The stable gut-brain axis is particularly impacted by TBI resulting in dysautonomia, gut-barrier dysfunction, and immune cell and microbiome structural variations. TBI prompts structural alteration to the intestinal villi and epithelium by vague mechanisms, damaging tight junctions (TJs) and following TBI-associated complications. Brain-derived DAMPs activate local macrophages to lead to the secretion of tumor necrosis factor-alpha (TNF-α), which impairs TJ function and increases gut permeability, as demonstrated in TBI fly models. In general, primary and secondary injuries result in complex pathogenesis that causes transient or permanent deficits [38–40] (Fig. 1).

Innate and adaptive immune responses to TBI

The innate immune response is the initial response to injury, but cells of the adaptive immune system quickly migrate and activate by inducing adhesion molecules on the BBB, releasing chemokines, and expressing co-stimulatory molecules on microglia [41]. The inflammatory response to TBI initiates tissue injury and results in DAMP secretion [42]. DAMPs are recognized by Pattern Recognition Receptors (PRRs) such as Toll-like receptors (TLR) on dendritic and myeloid cells, leading to pro-inflammatory cytokine production by direct intracellular signal transduction or by inflammasome formation (NLRP1 and NLRP3) [43]. High HMGB1 levels and other DAMPs such as S100b are related to poor clinical outcomes post-TBI [44, 45]. Studies involving murine models have shown that suppression or knockout of TLR-4, a main microglial receptor for HMGB1, decreases cerebral edema and cortical IL-6 release [46] Additionally, administration of. anti-HMGB1 monoclonal antibodies have shown anti-edema effects in rats with TBI [47]. Inflammasomes are protein complexes found within the cytosol and are primarily present in the central nervous system (CNS) where they are expressed by astrocytes, microglia, and macrophages. They cleave and activate pro-inflammatory caspases triggering cytokine activation (e.g. IL-1β or IL-18) [43].

Poor clinical outcomes are associated with upregulation of NLRP3 inflammasomes [48]. Animal studies have shown that targeting this cascade can be beneficial. NLRP3 deficient mice exhibit less histological brain damage, lower caspase-1 levels, and consequently lower levels of IL-1β in brain lysate. In murine studies, IL-1β was associated with improved cognitive function post-TBI when compared with wild-type mice [49]. The over-expression of pro-inflammatory cytokines (IL-1β, IL-6, IL-18, and TNFα) is the leading consequence of tissue injury, DAMP release, and inflammasome activation [50]. Likewise, glial and neuronal cell damage leads to the synthesis of various chemokines including IL-8, MCP1, and CCL5 [51], which attract and activate peripherally-derived and CNS-resident immune cells (microglia, neutrophils, and T-cells) to the injured site [41]. Several studies have reported a relationship between prominent pro-inflammatory cytokine responses and poor outcomes [50, 52], along with genetic studies highlighting that polymorphisms in cytokine genes (IL-1β and TNF α) also determine outcomes [53].

Within hours of a TBI, the IL-8 chemotactic gradient and upregulation of vascular endothelium cell adhesion molecules (E-selectin and Intercellular Adhesion Molecule 1 (ICAM-1) assist in neutrophil migration to injured tissue. This neutrophilic peak is predominant for day 2; then, numbers decrease, and other cells like monocyte-derived macrophages, natural killer cells, and T lymphocytes infiltrate and activate resident CNS microglia [41]. Although neutrophil recruitment to injured tissue can be beneficial through the elimination of cell debris [54], it can also have negative effects such as direct toxicity to neurons by matrix metalloproteinases, ROS, and TNF-α [55]. Increased vascular permeability can also cause edema and subsequent cellular metabolic stress [41].

The activation of microglia is a reaction triggered by the binding of DAMPs to TLRs after a CNS injury. It occurs promptly following the initial decline in neutrophil response as demonstrated in mice and human TBIs [56]. In murine models, microglia/macrophage activation occurs within 24 h post-injury [57]. Several studies have reported a predominant M2-like phenotype 1-week post-injury, which shifted to an M1-like phenotype in a second peak 1-month post-injury. Despite this phenotypic pattern, it is noteworthy that the majority of activated microglia display mixed characteristics/differentiation [58–61]. In addition

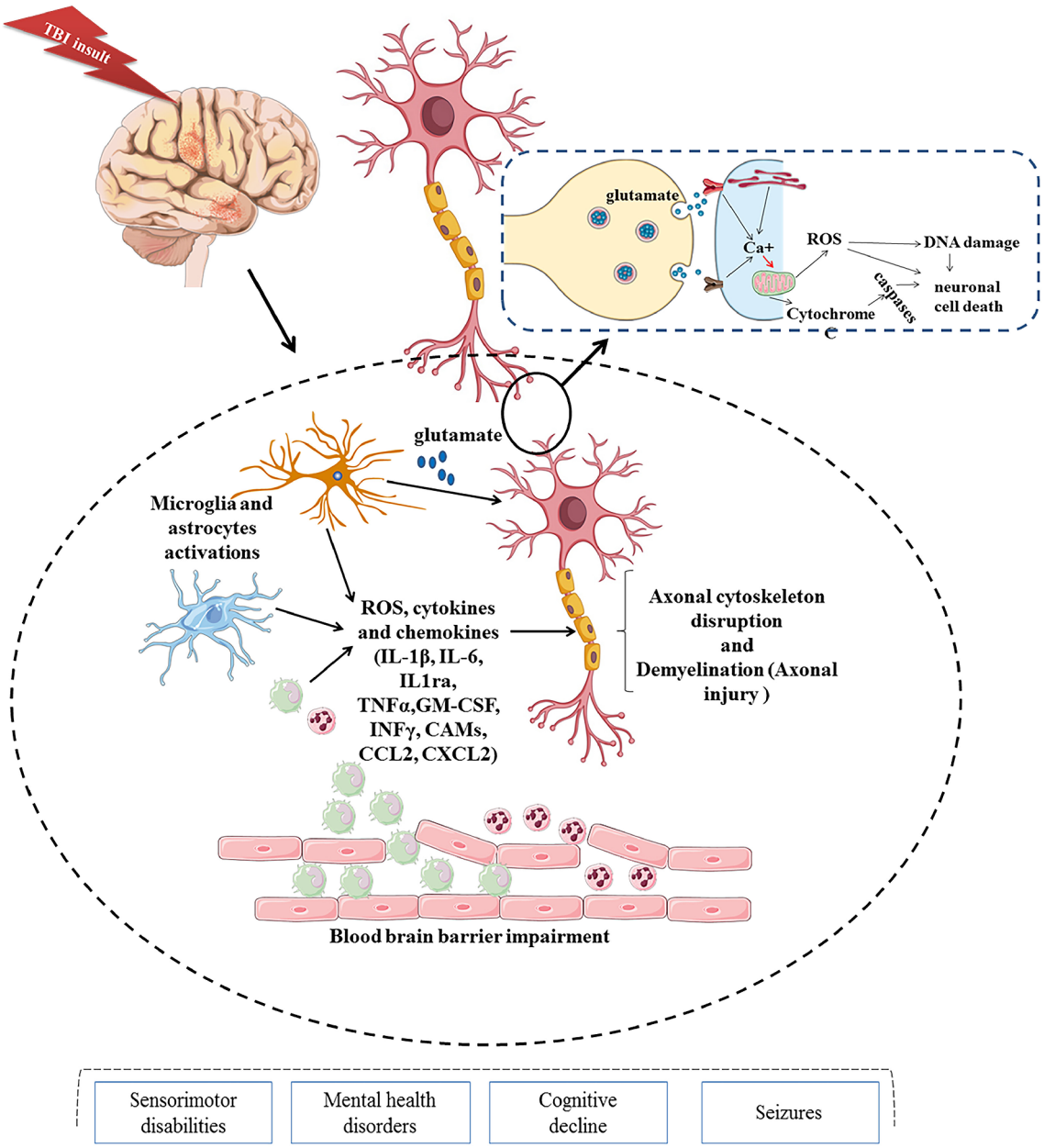

Fig. 1 Pathophysiology of traumatic brain injury [Traumatic brain injury (TBI), reactive oxygen species (ROS), calcium (Ca^2+), Tumor necrosis factor-alpha (TNF-α), Interferon-gamma (IFN-γ), interleukin (IL), Granulocyte-macrophage colony-stimulating factor (GM-CSF), C-C motif chemokine ligand 2 (CCL2), C-X-C motif chemokine ligand 2 (CXCL2), Cell adhesion molecules (CAMs)]

to local microglia activation, peripherally-derived monocytes/macrophages migrate to the injured site and undergo similar differentiation in terms of the M1/M2 pattern [62, 63]. Furthermore, TBI induces the release of peripherally derived cerebral antigens into the circulatory system, lymph nodes (through lymphatics, a perivascular system of waste clearance channels), and possibly also via meningeal lymphatic vessels where naïve immune cells prompt adaptive autoreactivity.

DAMPS can initiate adaptive autoimmunity by directly maturing immature dendritic cells (DCs) into mature and active DCs, which present self-antigens and stimulate naïve T-cells. Simultaneously, with the recruitment of monocytes/macrophages, T-cells migrate into the site of injury as a result of the upregulation of cell adhesion molecules and chemokine production. Although the contribution of autoreactive T-cells to autoimmune diseases like multiple sclerosis is well-documented, their specific role after CNS injury remains unclear [41].

Seven days post-injury, patients with TBI exhibit high concentrations of activated B-cells that are characterized by increased memory (CD27+) and class-switched memory

(CD27 + IgD-), suggesting germinal center (GC) generation by T cell-dependent immune responses [41, 64]. Several autoantibodies to cerebral proteins, including cytoskeletal structures and neurotransmitter receptors are reported in humans post-TBI. Studies suggest that TBI likely results in a polyantigenic response. The initial temporal pattern of immunoglobulin production is a short-lived IgM response, followed by more prolonged IgG production. Notably, the IgG response persists many years after injury, indicating persistent antigen exposure and the potential relevance of these autoantibodies in the chronic phase of TBI, rather than their being harmless bystanders [41] (Fig. 2).

Statins

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, commonly referred to as "statins", are prescribed as hypolipidaemic agents in the clinic. Their mechanism of action involves binding to the active site of HMG-CoA reductase, inhibiting substrate binding and subsequently blocking cholesterol biosynthesis [65]. Statins are widely used to reduce low-density lipoprotein (LDL) concentrations and decrease cardiovascular risk [66]. Additionally, they have several beneficial pleiotropic effects, including anti-oxidant, anti-excitotoxicity, anti-inflammatory, and anti-thrombotic activity, as well as endothelial and vasoactive properties, immunomodulatory potential, and promotion of angiogenesis, neurogenesis, and synaptogenesis to modulate parenchymal damage in TBI (as shown in Table 1) [13, 27, 28, 67–69]. Moreover, statins could be considered viable options as TBI therapies due to their existing Food and Drug Administration (FDA) approval, broad accessibility, and well-documented adverse event profiles.

Statins fall into those that are fungal-derived (lovastatin, simvastatin, and pravastatin) and those that are synthetic (atorvastatin, cerivastatin, fluvastatin, pravastatin, pitavastatin, and rosuvastatin) [65, 70]. These lipid-lowering agents bear different structural and physical properties, leading to two groups based on their hydrophobicity

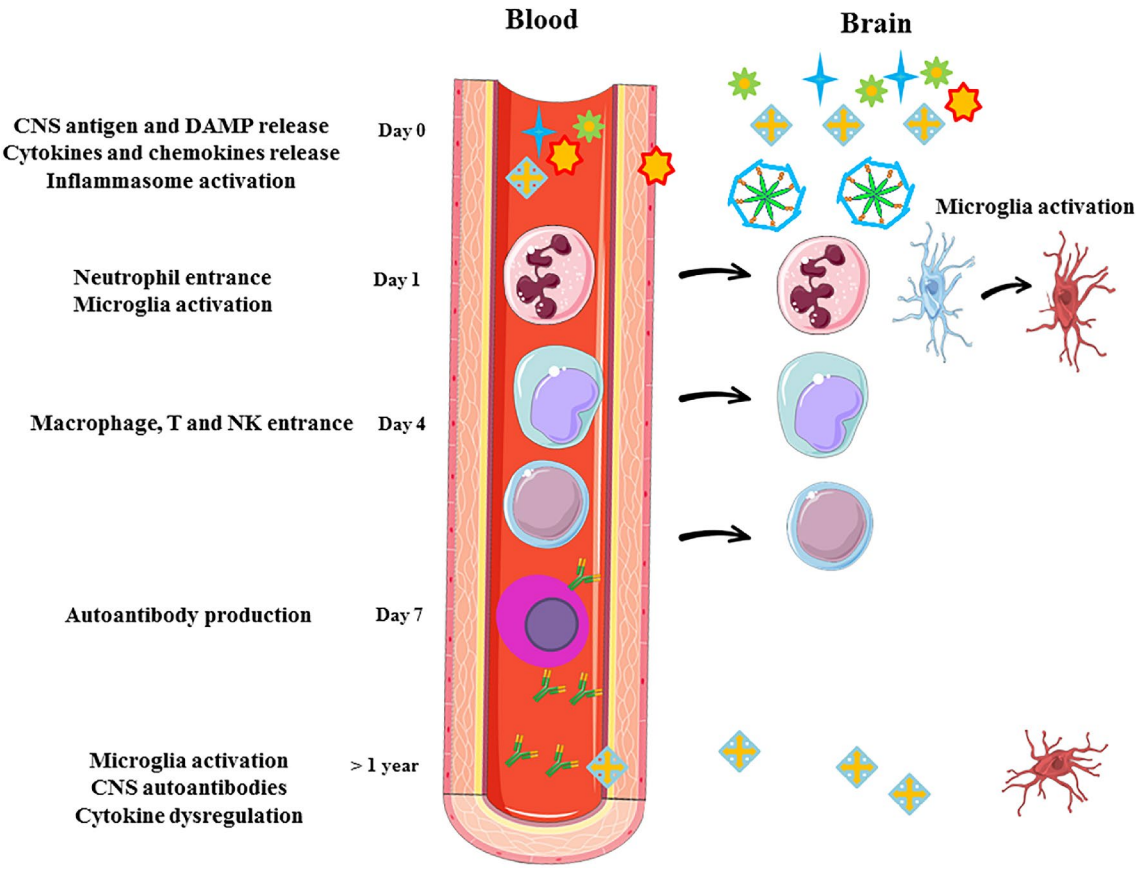

Fig. 2 Schedule of inflammatory response in TBI: at first CNS antigen and DAMP release occur and quickly followed by inflammasome activation and cytokine/chemokine production, which lead to attraction and activation of immune cells. This cellular recruitment initially comprises exclusively innate immune cells, but adaptive leukocytes are added within days. While this response mainly diminishes, a percentage of patients show a constant immune dysregulation, consists microglial activation, cytokine dysregulation, and constant autoantibody generation [Central nervous system (CNS), Damage-associated molecular patterns (DAMPs), Natural killer cells (NK), T lymphocyte (T)]

Table 1 The protective effect of statins in traumatic brain injury

Summary of neuroprotective effects of statins in TBI
Anti-neruroinflammation
↓ Inflammatory cytokines & chemokines
↓ Oxidative stress
↓ Microglial activation
↓ Cerebral edema
↑ BBB integrity
Anti-apoptosis
↑ Bcl-2
↓ Caspase
Anti-edematous
↑ claudin-5
↓ ICAM-1
↓ PMN parenchyma infiltration
↓ BBB permeability
Cerebral blood flow
↑ eNOS
↑ Endothelial integrity
↓ VWF
↑ endothelial integrity
↓ Microthrombosis
↓ Platelet activity
Neurogenesis
↑ PI3K/Akt
↑ VEGF
Angiogenesis
↑ VEGF, VEGFR2
↑ PI3K/Akt, eNOS
Synaptogenesis
↑ Synaptophysin

Blood-brain barrier (BBB), Intercellular adhesion molecule-1(ICAM-1), polymorphonuclear leukocytes (PMN), Vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR-2), Endothelial isoform of nitric oxide synthase (eNOS), Von Willebrand factor (vWF)

(Table 2). Structural and physicochemical differences cause variation in pharmacokinetic features, and could, in turn, affect their pharmacodynamics and therapeutic effects [65]. While lipophilic statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin) passively cross the BBB, both in vitro and in vivo reports document that hydrophilic statins can also enter the neuroparenchyma [71].

The protective effect of statins in traumatic brain injury

Anti-neruroinflammation

Astrocyte and microglia activation, and subsequent TNF-α production, are signs of neuroinflammation observed in post-TBI brains [72, 73]. TNF-α can induce both apoptosis and survival signaling in neurons through TNF-α receptor 1/2 (TNFR1/TNFR2) [74, 75]. As mentioned earlier, neuroinflammation plays a significant role in the exacerbation and outcomes of TBI. Simvastatin has been shown to exhibit anti-inflammatory activity, which has been proven to be neuroprotective in both transient and permanent experimental TBI studies [76, 77]. Furthermore, it has been documented in the literature that the neuroprotective effects of statins may be independent of their serum cholesterol-lowering action [78, 79]. Chong et al. conducted studies in TBI rats and reported that simvastatin has neuroprotective effects on pre-existing hypercholesterolemia, likely due to its anti-neuroinflammatory activity rather than its cholesterol-lowering activity. They found that the use of simvastatin in the acute stages following a TBI reduced astrocyte and microglia activation, neuronal TNFR1 activation, neuronal apoptosis, and TNF-α expression in rats with pre-existing hypercholesterolemia [80]. Another study demonstrated that both simvastatin and atorvastatin suppressed parenchymal inflammatory cytokine mRNA expression, reduced hippocampal degeneration, and improved functional neurological deficits after TBI in mice [81].

Other neuroprotective effects of simvastatin are related to its anti-inflammatory action on vascular endothelial inflammation [76], the TLR4/ NF-kappaB pathway in an injured rat brain [77], and attenuation in astromicroglia as well as hippocampal TNF-α expression [73].

Wang et al. have indicated that administration of simvastatin after injury decreases cerebral vascular endothelial cell activation via suppression of ICAM-1 expression, and ameliorates functional and histological outcomes in TBI experimental models [76]. Additionally, simvastatin administration noticeably prevented mRNA and protein expressions of TLR4, NF-κB, and downstream inflammatory factors, including interleukin-1β (IL-1β), TNF-α, IL-6, and intercellular adhesion molecule-1 (ICAM-1). Simvastatin treatment following TBI significantly improved secondary

Table 2 Pharmacokinetics of statins

characteristic	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Lipophilicity	Lipophilic	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
Half-life	14 h	2.3 h	3 h	12 h	2 h	19 h	3 h
Excretion (Renal) (%)	<2	6	10	2	20	10	13
Excretion (Faecal) (%)	>98	93	83	79	70	90	60

Data summarised from [65, 71]

brain damage, such as brain edema, BBB impairment, cortical apoptosis, and motor deficits [77].

Xu et al. reported interesting data regarding atorvastatin's neuroprotective effects in TBI through its anti-inflammatory and immunomodulatory activities.]. These effects are attributed to the alteration of peripheral leukocyte subset invasion and microglia/macrophage polarization status. Acute atorvastatin therapy at the injury site reduces the recruitment of natural killer cells, neutrophils, and T cells, as well as the production of chemokines (RANTES and IP-10) and pro-inflammatory cytokines (IFN-γ and IL-6). Interestingly, this therapy choice also increases the concentrations of regulatory T cells (Tregs) in the peripheral spleen and brain, along with their major effector cytokines IL-10 and TGF-β. Atorvastatin significantly reduces total microglia/macrophage activation but enhances the M2/M1 ratio by inhibiting M1 polarization and enhancing M2 polarization. Furthermore, it leads to reduced neuronal cell death and improved behavioral deficits [82]. .

Findings by Chen et al. also indicate that lovastatin's protective mechanisms in the TBI brain may be attributable to dampening of the inflammatory response. Pre-administration of lovastatin in a rat model recovered functional outcomes and attenuated the extent of brain damage by decreasing IL-1β mRNA, TNF-α, and protein tissue levels [83]. Moreover, Sánchez-Aguilar et al. reported that a double-blind, randomized clinical trial (DB RCT) in patients with moderate to severe TBI suggested that rosuvastatin potentially induces anti-inflammatory effects and promotes recovery after TBI [84].

Rosuvastatin has also been shown to inhibit TBI-induced intestinal injury in rat models, potentially through the blockage of the CD40/NF-κB pathway [85]. Organ dysfunction, particularly in the gastrointestinal system, is frequently observed in TBI patients [86]. Studies have indicated that TBI increases intestinal CD40 expression, nuclear factor (NF)-κB activation, and pro-inflammatory cytokine production, which contribute to the development of acute intestinal mucosal injury [85].]. Rosuvastatin has been found to partially suppress CD40 expression, attenuate NF-κB activation, and reduce IL-1β and TNF-α concentration. Furthermore, histopathological assessment has demonstrated that rosuvastatin improves TBI-induced damage to the jejunal structure [85, 87–89].

Vascular and endothelial effects

Brain edema after TBI is a considerable causative factor for patient morbidity and mortality [90]. It is described as enhancement of brain volume due to a localized, or spread-accumulation of fluid in the brain parenchyma [91]. In the acute TBI phase, edema is partially related to BBB disruption resulting directly from the traumatic injury or linked to abnormal brain function, astrocyte dysfunction, inflammatory-related mechanisms, and metabolic disturbances occurring as a response to injury [92]. BBB integrity is mainly determined by the tight TJs and adherens junctions (AJs) between endothelial cells. Post-traumatic neuroinflammation is harmful with potentially altered junction protein expression, - resulting in increased paracellular permeability, leukocyte infiltration, and edema [93].

Claudin-5 is a crucial component of TJs, and its absence is associated with in vitro BBB breakdown [94, 95]. Following TBI, there is a decrease in claudin-5 expression at 24 h post-injury, but simvastatin has been shown to counteract this by increasing claudin-5 levels [90]. Brain edema is also linked to the infiltration of polymorphonuclear leukocytes (PMN) through ICAM-1 expression. Mice deficient in P-selectin and ICAM-1 exhibit reduced brain edema following TBI [96]. Beziaud et al. demonstrated that simvastatin reduces post-TBI ICAM-1 expression and PMN infiltration in the brain parenchyma. This reduction may inhibit the release of proinflammatory mediators and prevent BBB alterations. Therefore, simvastatin decreases cerebral edema within 24 h of TBI by reducing BBB permeability, ICAM-1 expression, neutrophil parenchyma infiltration, and enhancing claudin-5 expression [90]. Other studies investigating the administration of simvastatin and atorvastatin administration have also reported their anti-edematous effects after TBIs [77, 97, 98].

The vascular endothelium controls smooth muscle tone by NO which is generated by three various isoenzymes: endothelial form (eNOS), neuronal form (nNOS), and the inducible form (iNOS) [99, 100]. eNOS is expressed in cerebrovascular endothelium and leads to vasodilation. Statins can upregulate eNOS, independent of their serum cholesterol activity. Statin treatment has been reported to enhance eNOS mRNA, protein, and enzymatic activity, increasing cerebral blood flow. However, reported findings vary as Wible et al. showed decreased eNOS RNA levels in a murine TBI model, and eNOS RNA levels were unchanged with statin exposure [28]. In addition, decreased NO levels have been observed following simvastatin therapy as demonstrated by Yüksel et al. [100].

Simvastatin treatment ameliorates neuropathological changes of diffuse axonal injury in the acute stages of experimental TBI through reduced NO and vascular endothelial growth factor (VEGF) levels and inhibiting the development of vasogenic brain edema [100]. BBB deterioration in a hypoxic environment is multifactorial, and linked to elevated NO and VEGF levels [101]. NO synthesized by iNOS has harmful effects after TBI by promoting BBB permeability and edema [100]. Blood vessels exposed to VEGF have increased permeability, and are associated with

cerebral edema and ischemic damage compared to normal/unexposed blood vessels [101]. Zhang et al. reported that VEGF boosts vascular permeability by provoking NO synthesis and release. Reduction of BBB permeability is possible by inhibiting VEGF in the acute stages following brain damage [102]. Thus, Simvastatin reduces vasogenic brain edema and BBB leakage by reducing NO and VEGF.

Statins also diminish intravascular thrombosis in TBI models. Posttraumatic intravascular coagulation that results in thrombosis can be the main cause of secondary ischemia after TBIs [103, 104]. Animal studies demonstrate that delayed thrombosis occurs in the hippocampal CA3 region and lesion boundary zone at 1–4 h post-injury, peaks at days 1–3, and then declines at days 8–15 [105, 106]. Intravascular thrombosis also happens in other parts of the cortex, corpus callosum, and striatum. Delayed thrombosis is comprised of fibrin, platelets, and von Willebrand factor (vWF). Atorvastatin treatment reduces plasma vWF levels and platelet activity and decreases delayed thrombosis after TBIs [106]. Atorvastatin can decrease pathological microvascular characteristics post-TBI and promote restoration of spatial memory function, thereby improving functional outcomes [105].

Anti-apoptosis

Statins decrease neuronal cell apoptosis, leading to enhanced neuronal function following TBI [77, 107, 108]. . Administration of statins in animal models has been shown to improve neuron survival. In addition to primary neuronal necrosis, delayed neuronal apoptosis occurs in the boundary zone of injured cortical sites and the hippocampal CA3 region in TBI animal models [109, 110]. Both pathways for neuronal cell death can lead to neuronal loss and deficits in neurological function in these areas [111]. However, these areas have the potential to be salvaged, and rescuing damaged neurons can lead to improvement in functional outcomes after brain injury [112]. Simvastatin treatment enhances Akt phosphorylation in post-TBI neuronal cells, which in turn phosphorylates downstream targets such as eNOS, Forkhead transcription factor 1, and inhibitory-κB, resulting in anti-apoptotic effects through the inhibition of caspase 3 activities [108]. Bcl-2 is an anti-apoptotic member of the Bcl-2 protein family. Simvastatin also up-regulates Bcl-2 gene expression and protein levels in neurons, leading to neuroprotection [113]. Atorvastatin can similarly rescue damaged neurons and/or increase their survival in these areas after injury, thereby reducing neurological functional deficits [114].

Reduction of excitotoxicity

An increase in extracellular glutamate concentration provokes the development of neurotoxicity, neuronal injury, and death [31, 115]. Statins have been shown to reduce glutamate excitotoxicity by altering cell cholesterol metabolism and activating TNF receptor 2 signaling. The decrease in membrane cholesterol can attenuate the release of glutamate from nerve terminals suggesting a potential mechanism for the neuroprotective activity of statins [116]. Simvastatin has been found to decrease glutamate excitotoxicity by reducing the association of NMDA receptors with lipid rafts [117]. Additionally, the neuroprotective effect of lovastatin against glutamate-excitotoxicity has been attributed to the activation of TNF-R2 signaling pathways as demonstrated by Dolga et al. [118].

Neurogenesis

Besides protecting against neuronal apoptosis post-TBI, some data suggests that statin therapy promotes new neuron growth and differentiation. Neurogenesis defines a generation of new neurons in the CNS through the division of neural stem cells (NSC). Most neurogenesis happens at the initial stages of development, specific brain regions preserve neurogenesis across the lifespan, encompassing the dentate gyrus (DG) of the hippocampus and the subventricular zone lining the lateral ventricles [119, 120]. Xie et al. showed that simvastatin promoted post-TBI neurological functional recovery possibly via increased Notch-1 expression, Notch signaling activation, and augmenting neurogenesis at the injured site [121]. Notch-1, a cell surface receptor, determines cell fate, and it may also determine the synaptic plasticity of adult brains [122, 123]. Suppression of the Notch pathway via γ-secretase inhibitors attenuated the effects of simvastatin. Thus, simvastatin-induced NSC proliferation may be linked with Notch signaling pathway activation. Extended NSC proliferation and neurogenesis following simvastatin therapy might be one of the underlying mechanisms behind its beneficial therapeutic effects on neurological recovery in TBI rat models [121].

Cognitive deficits and motor dysfunction are frequent and highly disabling features in brain trauma survivors, with learning disability and memory loss the most prevalent cognitive impairments among those with severe head injuries [124, 125]. It has been shown that statin treatment improves spatial learning 31–35 days after TBI onset in animal TBI models. On the other hand, statins stimulate new cell generation (neurogenesis) in the DG at days 15 and 35 post-TBI. Neurogenesis may be related to the recovery of spatial learning due to the concurrence of spatial learning recovery with neurogenesis [107]. To form functional neurons

from newly generated cells, the following must occur- differentiation, maturation, migration, and formation of new synapses [107, 126, 127]. It takes four weeks to complete these steps [127]. Statin treatment considerably enhances the quantity of NeuN/BrdU-co-labeled cells compared to TBI + saline groups, suggesting that statin therapy enhances differentiation into mature neurons [107, 128]. Following electrophysiological studies, it has been shown that newly generated cells migrating into the granular zone have the potential to function as mature neurons [107, 129]. Therefore, spatial learning recovery that occurs in week five after a TBI may be due to the aforementioned steps [107].

Angiogenesis

Angiogenesis is a critical determinant of functional outcome post-TBI [130]. Statins have been shown to promote angiogenesis in the injured brain. Endothelial progenitor cells (EPCs) are a type of stem cell that contribute to the construction of new blood vessels in postnatal vasculogenesis and angiogenesis [131]. These cells are typically found in the bone marrow and migrate to the peripheral blood in higher concentrations following a TBI. The levels of circulating EPCs in the peripheral blood EPC levels peak at 48 h and return to normal after day seven [132]. The concentration of circulating EPCs has been associated with the severity of prognosis.

Atorvastatin therapy enhances the circulation and mobilization of EPCs in the TBI model promoting angiogenesis and vasculogenesis [131]. This has been shown to cause atorvastatin-induced functional outcomes in TBI rat models [114, 131]. Also, others have shown that simvastatin promotes angiogenesis [107, 128, 133]. Simvastatin has even been shown to heighten TBI-induced angiogenesis by enhancing endothelial cell proliferation and vascular length. It stimulates VEGF expression [128] an important protein for angiogenesis activation [134]. Also, it further increases VEGF receptor (VEGFR-2) concentrations at the injured cortex [133]. VEGF binds to VEGF-2 (flk-1) on endothelial cell surfaces inducing intracellular tyrosine kinases and activating numerous downstream triggers for angiogenesis [134]. Microvascular permeability, endothelial cell proliferation, migration, and survival are mediated by downstream activation of VEGFR-2 via VEGF. Signals for example for Akt-dependent eNOS phosphorylation occur via intracellular signaling pathways, including the Raf-Mek-Erk and the PI3K/Akt pathway. These are pivotal for angiogenesis. Reinforced p-eNOS stimulates angiogenesis promoting mural cell infiltration of immature angiogenic branches. This indicates that simvastatin induces phosphorylation of eNOS in a VEGFR-2/ PI3K/ Akt-dependent pathway and highlights the significant role of eNOS in simvastatin-induced angiogenesis following TBIs [133].

Synaptogenesis

Considerable neuronal damages occur in ipsilateral hippocampal formation following cortical contusion, disrupting normal neuronal activity. The CA3 pyramidal neurons are disrupted by this injury, causing Schaffer collaterals, resulting in partial CA1 regio superior dendritic field deafferentation. Following a TBI, CA1 long-term potentiation (LTP), a key synaptic event for learning and memory, undergoes substantial changes. TBI rat models have shown considerable changes in hippocampal synaptic transmission 15 days after an injury. Such changes may be causative factors behind learning and memory deficits [135]. Neurotrophic factor upregulation and neurogenesis are also linked to augmented synaptogenesis. Synaptophysin, associated with presynaptic terminals is also reduced in the peri-contusional cortex. Atorvastatin administration enhances synaptophysin staining of the ipsilateral and hippocampal CA3 region, demonstrating either protective action against secondary synaptic injury, or an enhanced synaptogenesis [114]. Moreover, Wu et al. outlined that simvastatin elevated synaptophysin density in the ipsilateral hemisphere, resulting in elevated axonal and synaptic density after a TBI [136].

Reduction of axonal injury

Simvastatin administration in experimental TBIs has been shown to decrease axonal injury, increase neurite outgrowth, and promote neurological functional recovery. Simvastatin may induce neurite outgrowth by manipulating the PI-3 K/Akt/mTOR and PI-3 K/GSK-3b/APC pathways [136]. Additionally, combination treatment with simvastatin and other agents such as erythropoietin and niaspan has been found to improve axonal damage following CNS injury [137, 138].

Clinical statin treatment in TBI

Preclinical models demonstrate the benefits of statin treatment in TBI. However, there is limited clinical data available (Table 3). Lokhandwala et al. found that TBI patients who were receiving statins before the injury showed better neurological improvement compared to matched controls. The statin-treated patients had a lower percentage of in-hospital mortality, skilled nursing facility disposition, and a higher median Glasgow Outcome Scale (GOS)-extended score [139].

In Shafiee et al. DB placebo-controlled RCT on patients with severe TBI, oral simvastatin therapy (40 mg, daily) for

Table 3 Randomized clinical trials of statins in traumatic brain injury

Reference (Date)	Trial design	Sample size & TBI severity	Stain therapy design	Outcomes
Shafiee [140]	Double-blind placebo-controlled randomized clinical trial	98 patients with severe TBI	Simvastatin (40 mg, daily) for 10 days	↑ Glasgow Coma Score (ns) ICU stay (ns) neurosurgery ward stay (ns) mechanical ventilation length
Soltani [141]	Double-blind, randomized clinical trial	60 patients with moderate to severe TBI	Atorvastatin (40 mg, daily) until hospitalization in the ICU	↓ CRP ↓ ESR ↓ white blood cells ↓ ICU stay ↑ Glasgow coma score
Robertson [143]	Randomized clinical trial (Phase II)	52 patients with mild TBI	Atorvastatin (1 up to 80 mg/kg, daily) for 7 days	(ns) PCS (ns) PTSD (ns) depressive symptoms cognition (ns) memory status (ns) verbal fluency (ns) functional status (ns) work status
Farzanegan [142]	Randomized clinical trial	65 patients with moderate to severe TBI	Atorvastatin (20 mg, daily) for 10 days	↑GOS ↓ MRS ↓ DRS
Sánchez-Aguilar [84]	Double-blind randomized clinical trial	36 patients with moderate to severe TBI	Rosuvastatin (20 mg) for 10 days	↓ disability scores ↓ TNFα
Tapia-Perez [145]	Double-blind randomized clinical trial	21 patients with moderate TBI	Rosuvastatin (20 mg) for 10 days	↓ amnesia time

Intensive care unit (ICU), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), post-concussion symptoms (PCS), post-traumatic stress disorder (PTSD), Glasgow Outcome Score (GOS), modified Rankin scale (MRS), Disability rating Scale (DRS), Tumour necrosis factor α (TNFα)

10 days led to a considerably greater Glasgow coma scale (GCS) score at discharge and one month after discharge. However, it did not show notable differences between the two cohorts in terms of duration of mechanical ventilation, intensive care unit (ICU) and neurosurgery ward stay [140].

Another DB RCT by Soltani et al. evaluated atorvastatin in moderate to severe TBI and showed improved GCS in TBI patients. It appears that atorvastatin therapy may decrease inflammatory factors as evidenced by lower levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cells in the atorvastatin group compared to controls respectively on the 14th day of hospitalization. Atorvastatin therapy also decreased the ICU stay of the treated group [141].

Farzanegan et al. conducted an RCT on 65 patients with moderate (GCS: 9–13) to severe (GCS: 5–8) TBI. Atorvastatin treatment showed significantly better functional outcomes as measured by GOS, modified Rankin scale (MRS), and Disability Rating Scale (DRS) scores three months post-injury compared to placebo. However, atorvastatin did not affect reducing the contusion expansion rate [142].

Although another trial by Robertson et al. of atorvastatin presented the safety of atorvastatin administration for 7 days post-injury, it did not show significant changes in neurological recovery after mild TBI [143]. Also, a different retrospective case-control study by Neilson et al. in an Asian population with severe TBI did not show a significant improvement in mortality or GOS between statin therapy and the control group [144].

Finally, a small prospective RCT using rosuvastatin exhibited a decline in amnesia time; however, no effect on disability three months following moderate TBI (GCS = 9–13) was observed [145]. This study was followed by a DB RCT comprising moderate and severe TBIs and revealed lowered TNFα levels and disability scores at 6 months [84].

In addition to clinical trials, there have also been large retrospective studies conducted in this field, which have reported promising results. Khokhar et al. conducted a retrospective cohort study on 100,515 patients aged 65 years and older, which reported that the use of statins after TBI led to a decrease in mortality following hospital discharge, as well as a decrease in the incidence of stroke, depression, AD, and related dementias [146]. Another retrospective cohort study by the same research group, this time on 112,109 patients aged 65 years and older, also observed a considerable reduction in in-hospital mortality after TBI. However, these positive findings need to be validated in randomized controlled trials to better understand the effect of statins [147]. Additionally, a cohort study assessing 28,815 patients following concussion reported that statin usage caused a significant reduction in the risk of developing dementia [148].

Discussion

TBI remains an outstanding and universal public health issue for which there are unmet clinical treatment needs. Despite substantial research with the use of cellular and animal models of brain injury, no therapeutic approach has been effectively transferred from the laboratory to the bedside. One cause for this might be a focus on therapeutic approaches targeting a single event or pathology, for example, intracellular calcium overload [107, 149]. However,

various pathological mechanisms are implicated in brain injury after TBI, including inflammation, oxidative stress, BBB disruption, ionic disturbance, excitotoxicity, mitochondrial dysfunction, neuronal necrosis, and apoptosis [27, 31]. Consequently, an efficient therapy should demonstrate actions that will impede or cut down secondary injury and magnify endogenous neuroplasticity. Treatments that target a single pathological mechanism after TBI are inadequate to achieve considerable symptom amelioration and improved clinical outcomes. Therefore, using combination therapy or an agent (e.g., statins) that can affect numerous diverse pathological mechanisms is probably preferable to a single targeting treatment approach.

Statins have several beneficial pleiotropic effects that include anti-inflammatory, anti-oxidant, anti-excitotoxicity, anti-thrombotic, immunomodulatory effects, endothelial and vasoactive properties and promoting angiogenesis, neurogenesis, and synaptogenesis in TBI [13, 27, 28, 67, 69, 150–157]. Therefore, statins are an extremely suitable choice for TBI treatment and offer a strategy for affecting multiple events associated with neuroprotection and neurorestoration following brain injury. Although the pleiotropic mechanisms of action, established history of clinical usage, and well-known side-effect profiles make statins appropriate for clinical application [158–160], several factors, such as ideal statin type and dosage regimen, have not yet been thoroughly defined.

Despite preclinical studies demonstrating that statins provide vigorous neuroprotective effects after TBIs, most early studies utilized non-FDA-approved supra-physiological doses that may also induce muscle or hepatic toxicity. There are differences in CNS penetration, metabolism, and potency among the HMG-CoA reductase-inhibiting drug class, and there is insufficient data to define the optimal use of statins for specific injuries [161]. The majority of extended studies have been retrospective in nature, and although clinical trials show promise, such studies are still limited in number. Larger clinical trials are required to determine the safety and efficacy of statins for clinical use in humans with TBI. Furthermore, additional research is necessary to assess the full dose-response, duration, administration route, and comparison of various statins in order to optimize treatment strategies.

Future perspectives

Clinical trials assessing the efficacy and safety of statins in TBI are still limited. Additional large-scale clinical trials are needed to establish the safety and efficacy of statins in patients suffering from TBI. Moreover, future studies should focus on evaluating the presence of any dose-response association, optimal treatment duration, administration route, and differing effects of various statins to optimize treatment strategies.

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Declarations

We declare that some parts of Figs. 1 and 2 were drawn using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/). This Figure was modified with text, markings, and annotation using Microsoft Office PowerPoint (version 2010).

Conflict of interest The authors declare that they have no competing financial interests that could have appeared to influence the work reported in this paper.

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