Review Article

Metabolic Modeling-Based Drug Repurposing in Statin: An Overview of Mechanistic Approaches in the Management of Craniocerebral Trauma

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Abstract

Drug repurposing, known as drug repositioning, is considered a method for redeveloping a compound to utilize in a distinctive illness, which is now becoming a progressively critical procedure for industrial researchers and the scholarly community. A large number of repurposed medicines have been discovered by chance in the lab or through the careful monitoring of drug action in the clinic and retrospective analysis of clinical findings. Additionally, statins are broadly used to treat hyperlipidemia and prevent cardiovascular disease although their application as the neuroprotective agents weakening secondary neurological harm is yet limited in traumatic brain injury (TBI). Their other non-cholesterol-mediated (i.e., pleiotropic) mechanisms of action include upregulating endothelial nitric oxide synthase expression, and enhancing neurogenesis and synaptogenesis, as well as anti-apoptotic effects, increased angiogenesis, and various antioxidant and anti-inflammatory mechanisms. Almost all studies have supported the potential role of statins in neuroprotection, and a few have particularly focused on their effects in traumatic brain injury models. The sulfonylurea receptor 1 (SUR1) protein is a regulatory component linked with pore-forming ion channels. Thus, ATP-sensitive potassium (KATP) channels are created, which can be demonstrated in pancreatic islet cells and certain neurons. Further, transient receptor potential melastatin 4 (TRPM4) is the second pore-forming subunit of SUR1. Upregulating SUR1 and opening SUR1-TRPM4 opening have been observed in the different models related to central nervous system (CNS) injuries such as TBI. Sulfonylurea drugs may prevent neuronal degeneration and improve post-TBI cognitive results by inhibiting the SUR1-TRPM4 channel.

Keywords: Repurposed drug, Mechanistic approaches, Craniocerebral trauma, Statins

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Introduction

Traumatic injuries involving the cranium and intracranial structures (i.e., brain, cranial nerves, meninges, and other structures). Injuries may be classified by whether or not the skull is penetrated (i.e., penetrating vs. non-penetrating) or whether there is an associated hemorrhage. The significance of this issue is more pronounced among middle and low-income countries, where risk factors for traumatic brain injury (TBI) are high, while healthcare systems are devoid of the facilities required to address relevant health outcomes (1). The clinical impact of TBI is highlighted not only by its high mortality rate [TBI contributes to a third of all injury-related deaths in the United States (2)] but by the significant long-term health complications reported by those who survive their injuries. However, changes that have been described in the surface phenotype of circulating monocytes post-TBI suggest that the latter is responsible. The selectin CD62L, which mediates initial tethering and rolling of marginated cells along the vessel wall, is expressed exclusively on CD14++16– classical monocytes These phenomena are characterized by terminal membrane depolarization given that the influx of synthetic Ca^{2+} and Na^{+} initiates self-digesting intracellular processes. The Ca^{2+} activates proteases, phospholipases, and lipid peroxidase (Px), along with elevating the intracellular concentration of free fatty acids and radicals. Oxidative stress processes play a significant role in the pathogenesis that is related to secondary brain injury after occurring TBI (2). Following TBI, analysis of the monocyte pool in its entirety has revealed significant increases in CD11b and CD62L surface density (3). Given the expression profiles of these two adhesion markers, this data suggests that it is the expansion of both the classical and intermediate subsets that drives the significant elevation in monocyte number observed post-TBI. Many studies have used antioxidants like N-acetyl cysteine, vitamins C and E, and even iron chelators to combat post-traumatic oxidative stress, the results of which are inconsistent and unconvincing (2-4). Despite significant strategies, none of the pharmacological interventions have demonstrated effectiveness in clinical trials so far. Therefore, the study seeks to find the medicines which are effective in neuroprotective, anti-neuroinflammatory, antioxidant, and protective against cerebral ischemia, and can weaken BBB degradation, improve vascular hemodynamics, and benefit mitochondrial dysfunction (3-5). The researcher identified that some drugs have different clinical therapies and new mechanisms along with their main usage. In the TBI, erythropoietin, atorvastatin, glibenclamide, and tumor necrosis factor (TNF) antagonists, which are off-label-used drugs or "repurposing drugs" (6) for this disease, can be addressed as the most important of these medicines. Accordingly, they can be applied in adjuvant approaches or elective treatments. The current study presents a brief outline of a few of such drugs.

While effective pharmacologic therapies have not yet been approved for the treatment of TBI, drug re-offering may help accelerate the identification of effective pharmacologic therapies. Limited human trials examining NAC have shown neuroprotective effects in mTBI patients. Additional preclinical animal studies on NACA, MINO, and PHEN have also demonstrated efficacy in neuroprotection and reduction of delayed sequelae from TBI. Future studies, especially those involving human trials, are needed to elucidate the benefits of these re-proposed drugs in reducing the acute and delayed effects of TBI.

Methods

Based on the reviewed studies, a large number of repurposed medicines have been discovered by chance in the lab or through the careful monitoring of drug action in the clinic and retrospective analysis of clinical findings. Statins are well tolerated, easy to administer, and have a long clinical track record in critically ill patients. Their side effects are well-defined and easily monitored. Preclinical studies have shown the significant benefit of statins in models of TBI and related disease processes, including cerebral ischemia, intracerebral hemorrhage, and subarachnoid hemorrhage. Multiple mechanisms have been defined by which statins may exert benefit after acute brain injury. Statins are currently positioned to be translated into clinical trials in acute brain injury and have the potential to improve outcomes after TBI (Figure 1).

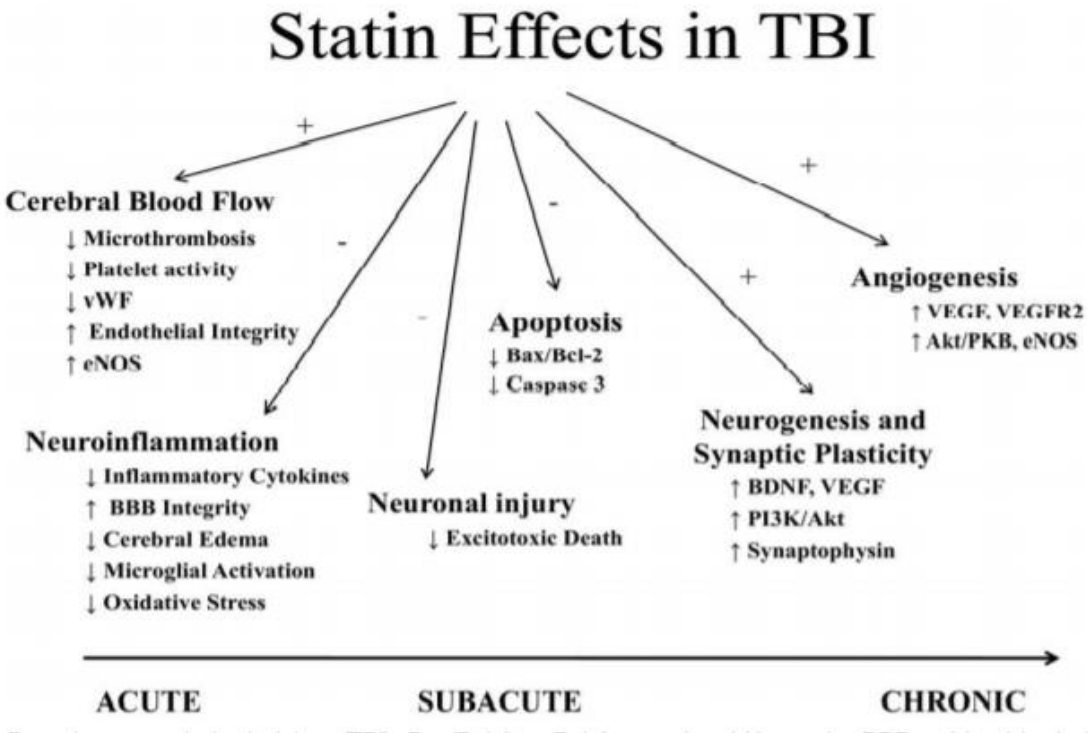

Figure 1. Shows the effects of statins in the treatment of brain trauma.

Studies related to the effect of statins and their derivatives in the treatment of traumatic brain injury (TBI). Studies that related to brain trauma, but in the process of their treatment, drugs other than statins and their derivatives were used, excluded from the study.

Classification of Statins: All statins contain an HMG-like component that binds to HMG-CoA reductase. Other molecular characteristics vary across the class, including potency, lipophilicity, metabolism, and pharmacokinetics. Lovastatin, pravastatin, and simvastatin are obtained from fungi; atorvastatin, rosuvastatin, fluvastatin, and pravastatin are synthetic. Statin potency refers to the degree of HMG-CoA reductase inhibition. Rosuvastatin is the most potent due to its ability to form multiple polar bonds with the HMG-CoA reductase enzyme. Atorvastatin is the next most potent, followed by simvastatin, fluvastatin, and pravastatin. Whether the statin potency is important in neuroprotection after TBI is unknown, as many of the proposed mechanisms are not related to HMG-CoA reductase inhibition. Pravastatin and rosuvastatin are hydrophilic due to polar groups, whereas lovastatin, atorvastatin, fluvastatin, and simvastatin are lipophilic.

Statin and TBI: Statins' role as neuroprotectors has attracted much attention, but there is a lack of research on the basic pharmacology of statins in the brain. A few studies have shown that statin lactones and acids pass the BBB. However, the active transport mechanisms of these acid forms are not understood. In addition, statins reduce the production of mevalonate, which is the precursor of isoprenoids and cholesterol. Therefore, the protective effects of statins may be due to reductions in isoprenoids, which decrease prenylated proteins, reduce cholesterol that can alter cell structure and function, lower dolichol and coenzyme Q-10 (CoQ-10), and effects outside of the mevalonate/isoprenoid/cholesterol pathway such as stimulation of B-cell lymphoma-2 (Bcl-2) gene expression (6).

Regarding pharmacodynamics, inhibiting the HMG-CoA reductase enzyme is regarded as the most popular mechanism of action in statin drugs. The

results of most studies indicated that statins function through several non-cholesterol-mediated mechanisms of action (i.e., pleiotropic), which can have more roles in neuroprotection compared to cholesterol-dependent ones. The upregulation of endothelial nitric oxide synthase (eNOS) expression, as well as anti-apoptotic effects, enhanced angiogenesis, various antioxidant and anti-inflammatory processes, and promoted neurogenesis and synaptogenesis are among the most crucial non-cholesterol-mediated mechanisms (7, 8).

Further, statins increase eNOS expression by upregulating the protein kinase Akt pathway (9, 10). Kureishi et al. assessed the effect of simvastatin on cultured human umbilical vein endothelial cells (HUVEC) and referred to the induction of Akt phosphorylation and eNOS activation by simvastatin. The activation of simvastatin-induced Akt is prevented when cultures are incubated with l-mevalonate (a metabolite of HMG-CoA reductase), representing the significance of the statin prevention of this enzyme in their effect.

Some studies have highlighted the anti-apoptotic actions of statins for their contribution to the amplification of the excitotoxicity mediated by glutamate-NMDA. Statins inhibit cellular cholesterol production via a lipid-mediated mechanism, especially neuronal failure induced by oxygen-glucose deprivation (OGD)/re-oxygenation through forming 4-hydroxy-2-nominal (4-HNE) (11). Lim et al. reported a significantly lower rate of 4-HNE in the cortical neuronal cell cultures from Sprague-Dawley rats after receiving simvastatin treatment. Furthermore, statins result in expressing prosurvival proteins like Bcl-2 and inhibit proapoptotic proteases such as caspase-3 from producing (12, 13). Some of the features desired with statin therapy include potent reversible inhibition of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the ability to produce large reductions in low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C), the ability to increase HDL cholesterol (HDL-C), tissue selectivity (which focuses on treatment effects), optimal pharmacokinetics that limits systemic bioavailability and offers once a day dosing, and a low potential for drug-drug interactions (14, 15). For example, Lu et al. used a controlled cortical impact (CCI) model related to TBI for the male Wistar rats given 1 mg/kg simvastatin or atorvastatin. According to the results of Morris water maze tests, the statin treatment enhances spatial training at 31-35 days following TBI and reduces neuron damage in the hippocampus CA3 area. Statins increase the proliferation and migration of endothelial cells because of producing more nitric oxide and upregulating vascular endothelial growth factor (VEGF) (15). Some researchers highlighted statins in a TBI rat model and found post-TBI with the statin-mediated upregulation of VEGF and higher recovery of spatial learning based on a changed Morris water maze task (16). However, no study has yet focused on the effects of statins on VEGF upregulation and angiogenesis in human trials to the best of our knowledge. Additionally, contradictory results have been obtained regarding the effects of statins on acute lesion volume in the animal models of TBI. For instance, the results of an animal study indicated a decline in contusion volume by 20% and FJB-positive degenerating neurons by 35% after pretreating with lovastatin before a CCI injury (17). However, the contusion levels of treated mice were not significantly different according to a separate analysis with simvastatin and atorvastatin following comparable significant reductions in inflammatory marker expression and enhanced cerebral hemodynamics (18).

In animal models, post-traumatic treatment with a statin has led to inconsistent results in terms of contusion volume. For example, some researchers detected no difference in this regard following the administration of oral atorvastatin for seven days after injury in rats. It is worth noting that functional deficiencies decrease, while neuronal survival, synaptogenesis, and angiogenesis improve. However, the same research team reported a diminution in intracranial hematoma volumes among the rats treated with atorvastatin eight days after an injury during the same year (19). Statins are associated with uncertain consequences in the acute process of injury, including the fact that contusion and hematoma volumes and hematoma absorption rates reflect various anatomical injuries (19). The antioxidant and anti-inflammatory activity are many of the strongest pathways for statin neuroprotection, which is less well-known. Stoll et al. (2005) claimed that statins prevent reactive oxygen

Table 1: Summary of Major Preclinical Studies Involving Statins.

References	Drug	Dose	Experimental Model	Outcome Measure	Effect
Kureishi et al. (2007)	Simvastatin	1.0μM	Cultured human umbilical vein endothelial cells	NO production	Simvastatin-induced Akt –mediated phosphorylation of eNOS, leading to NO production
Lim et al. (2006)	Simvastatin	0.1-25 μM	Primary cortical neuronal cultures from fetal Sprague-Dawley rats	4-HNE production (neuronal death marker)	Reduced formation of 4 -HNE in simvastatin-treated cells
Johnson-Anu na et al. (2007)	Simvastatin	0 .1μM	Primary cortical neuronal Cultures from El 6 -El 7 fetal C57Bl6 mice	Bcl-2 m R NA, caspase 3 activation	Increased Bcl-2 m R NA formation, reduced caspase 3 activation
Lu et al. (2007)	Simvastatin and atorvastatin	1 mg/kg	Male Wistar rats, CCI	Morris Water Maze, hippocampal neuronal loss	Improved spatial learning. reduced hippocampal CA3 neuronal loss, improved neurogenesis in the dentate gyrus
Lu, Mahmood, et al (2004) and Lu, Qu, et al (2004)	Atorvastatin	1 mg/kg	Male Wistar rats, CCI	Histological evaluation of boundary zone, functional evaluation	Reduced functional deficits, increased neuronal survival, and synaptogenesis in boundary zone, increased angiogenesis
Wang et al. (2007)	Simvastatin and atorvastatin	20mg/kg	C57BI /6J male mice, CHI	Histology, Rocorod Morris Water Maze Microglial marker, TNF, and I L-6 levels	Improved vestibulomotor function as assessed by Rotorod, less deficit on Morris Water Maze, decreased microglia l proliferation and recruitment, reduced levels of TNF and I L-6
Wu et al. (2008 a,b)	Simvastatin	1 mg/kg	Male Wistar Rats, CCI	VEGF and BDNF expression via ELISA	Elevated expression of BDNF and VEGF in the dentate gyrus
Chen et al. (2007)	lovastatin	4 mg/kg	Rats, CCI	Rotarod contusion volume, TNF and IL-1β levels	I Improved Rotarod Performance Reduced contusion volume decreased TNF and IL-Iβ levels
Chen et al. (2009)	Simvastatin	37.5 mg/kg	Adult male Wistar Rats weight-drop contusion	m RNA and protein expressions of multiple inflammatory cytokines	Reduced expression of IL-1β, TNF, IL-6, ICAM-1
Ifergan et al. (2006)	Lovastatin and simvastatin	10-9-10-5 M	Human BBB- derived endothelial cells	Diffusion rates Of bovine serum albumin and [(14) C]· sucrose. across human BBB- ECs	A 50-60% reduction in the diffusion rates, significantly restricts the migration of multiple sclerosis-derived monocytes and lymphocytes across the human BBB in vitro

species (ROS) production by interfering with the expression and activity of NAD(P)H oxidase. Further, statins decrease the adverse effects of free radicals by increasing lipid peroxidation, LDL cholesterol oxidation, as well as antioxidant enzymes with the above elevation in NOS expression (20, 21). They induce anti-inflammatory effects by reducing the formation of isoprenyl intermediates in cholesterol biosynthesis (7, 8). In the case of inflammatory chemokines and mediators, statins suppress their expression in a variety of preclinical animal models. Chen et al. administered simvastatin to a TBI rat model (weight drop test) and examined brain samples 24 hr following injury (22, 23). Desirable pharmacologic

properties of a statin include potency in inhibiting HMG-CoA, selectivity of effect or uptake in hepatic cells to increase inhibitory activity and reduce activity in nonhepatic cells, lower systemic bioavailability to minimize systemic adverse effects, prolonged elimination half-life, and absence of or minimal metabolism via the CYP 3A4 system. Among the statins, rosuvastatin would appear to have the most favorable overall profile, at least concerning the features considered in this paper. In terms of modifying lipid profiles, rosuvastatin produces the greatest reductions in LDL-C and non-HDL-C, as might be predicted from the drug's pharmacologic profile, and the greatest increases in HDL-C compared with other marketed statins.

This supports the non-cholesterol-mediated anti-inflammatory effects of statins, which are distinct from CNS effects. Given that the current study identified some of the same inflammatory chemokines in human TBI, the in vitro and preclinical evaluations of the anti-inflammatory effects of statin are mainly beneficial. In general, statins exhibit a range of cholesterol and non-cholesterol-mediated pharmacodynamic effects based on preclinical research (Table 1).

Statins and Cognitive Outcomes After TBI: Some human studies assessed the cognitive outcome, especially dementia after TBI. Khokhar et al. studied the relationship between post-TBI statin administration and mortality and different associated morbidities, including stroke, depression, AD, and related dementias (ADRD) in a retrospective cohort study (48). The study included 100,515 Medicare beneficiaries 65 years and older who survived a (TBI) hospitalization, 50,173 statin users, and 50,342 non-statin users. The authors concluded that any statin use was associated with decreased mortality ($p<0.05$). Any statin use was also associated with a decrease in Alzheimer's disease and related dementias (RR, 0.77; 95% CI, 0.73-0.81), and stroke (RR, 0.86; 95% confidence intervals (CI), 0.81-0.91), and depression (RR, 0.85; 95% CI, 0.79-0.90). Possible administration of other drugs during hospitalization, continuity of the statins, and lack of generalizability are limitations that faced this study.

Redelmeier et al. conducted a population-based double cohort study (49). The study included 28,815 patients (median age=76 years; 61.3% female) diagnosed with a concussion by the assessing physician. They excluded patients with severe TBI that required admission within two days of the head injury and patients with a history of dementia or delirium in the prior five years, 7058 (24.5%) patients received a statin; while 21,757 (75.5%) did not receive a statin. It was found that 4727 patients subsequently were diagnosed with dementia over a mean follow-up of 3.9 years, an incidence of one case per six patients. This showed a 13% reduced risk of dementia in patients who received a statin (relative risk, 0.87; 95% CI, 0.81-0.93; $p<0.001$). However, lack of generalizability was a limitation of this study as it included only older adults.

Li et al. published a retrospective cohort study of the association between the use of angiotensin-converting enzyme inhibitor (ACEI), simvastatin, beta-blockers, metformin, and the combinations of these drugs selected and the occurrence of probable AD after TBI (50). The study included 733,920 patients, 15.450 patients with a history of TBI, and 718,470 non-TBI patients, TBI patients were followed for up to 18.5 years. TBI was associated with dementia and possibly AD with an odds ratio (OR) of TBI initial occurrence of 1.25 (OR 1.25 [95% CI], [1.134-1.378]) and was statistically significant ($p<0.05$). ACEI + statins exhibited a significantly lower risk, with a hazard ratio (HR 0.35 [95%CI] [0.15-0.82]) ($p<0.02$) compared to statin + metformin cohort, and (HR 0.44 [95%CI] [0.15-0.82]) ($p<0.01$) in comparison to no treatment. Combining ACEI with statins and the small sample size of the group were the limitations of this study.

Statins in Survivors of traumatic brain injury: Several neuroprotective strategies are suggested to limit the negative impact and improve functional outcomes, which included neuro-repair strategies, infusion of mesenchymal stromal cells (MSCs), remote ischemic conditioning, as well as some medications such as sex hormones, melatonin, minocycline, and hyperoxia (51,52). Despite the attractiveness and promise of these interventions in in-vitro or animal studies, results in human randomized controlled studies have been generally disappointing. Among

medications that showed much promise in improving outcomes after TBI are statins (52-53). Several mechanisms were proposed for their beneficial effects in TBI including their ability to modulate the initial parenchymal damage in TBI, their anti-inflammatory effects, their modulating effects on excitatory neurotransmitters, and their effects in improving endothelial functions and reducing micro thrombosis, as well as promoting angiogenesis, neurogenesis and synaptogenesis (53). Administration of simvastatin in rats after TBI significantly increased the length of the vascular perimeter, promoted the proliferation of endothelial cells, and improved sensorimotor function after TBI. Simvastatin also stimulated endothelial cell tube formation and enhanced vascular endothelial growth factor receptor-2 (VEGFR-2) expression (54). In another rat model (16 rats), rosuvastatin administration before spinal cord ischemia reduced spinal cord tissue injury by increasing antioxidant enzyme levels and attenuating tissue necrosis (55). Similarly, administration of simvastatin to rats after spinal cord injury was associated with significantly better locomotor function recovery, better electrophysiological outcome, less myelin loss, and higher expression of brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor (56). In another study, feeding simvastatin, but not lovastatin, to mice subjected to TBI significantly improved spatial learning and memory and restored axonal integrity (57). Atorvastatin was also shown to induce angiogenesis, increase circulating endothelial progenitor cell levels, and improve functional recovery after TBI in rats (58). Lastly, simvastatin administered after TBI to rats has been shown to reduce cerebral edema and blood-brain barrier permeability (59).

Secondary aggravated bleeding following trauma:

The role of SUR1: Serial scans indicated the extension of the main hemorrhage among a significant percentage of patients with traumatic cerebral contusions during the acute period after the injury. This process (PSH), commonly known as the "blossoming" of injury, is resulted from microvascular dysfunction (32). Capillary insufficiency leads to petechial bleeding into the tissues around the primary-affected area; these hemorrhages coalesce over time, extending the initial contusion and allowing non-contiguous hemorrhages to emerge. Such regions of secondary hemorrhage exacerbate the original damage by promoting the effect of mass on the underlying brain. Further, blood produces free radicals, which are extremely toxic to neural tissue, especially white matter. Therefore, PSH is a particularly harmful secondary injury process (26, 38). The process was once considered to be created by the microvessels characterized at the time of injury leading to persistent bleeding, particularly concerning coagulopathy. Individuals with TBI typically undergo coagulopathy, which may be related to the tissue factors released from damaged cerebral tissue, which results in activating disseminated intravascular coagulation (DIC)and extrinsic coagulation pathways, although the connection is incomplete. A large number of TBI cases with PSH are non-coagulopathic, and PSH is not observed in other coagulopathic ones. Furthermore, factor VII is only effective in inhibiting PSH when applied in rare circumstances to correct coagulopathy (38-40). A molecular cascade is created which begins with transcription factors due to mechanical effect, making SUR1 overexpression, edema, and PSH. In this injury model, the kinetic energy conveys by the microvessels and shears tissues of initial trauma fracture at the center of damage, causing the main contusion instantly. The amount of kinetic energy accumulated in the surrounding area (i.e., penumbra) is inadequate to break the microvessels. However, protein specificity 1 (Sp1) and nuclear factor B are two mechanosensitive transcription factors, which are activated by kinetic energy (41, 42). Following the trauma, such transcription factors quickly translocate to the nucleus of penumbral endothelial cells, resulting in overexpressing the transcription factor of SUR1. Conversely, the channel unlocks when ATP is exhausted (since it is common in the injury situation), enabling salt to stream in. In addition, water is accompanied by sodium which causes oncotic swelling (i.e., cytotoxic edema). This cycle leads to capillary luminal narrowing in the penumbral endothelial cells, and consequently ischemia. Further, the ischemic penumbra condition upregulates SUR1 based on the effect of hypoxia-inducible factor 1 (HIF1) on Sp1. The cytoskeleton of endothelial cells changes when they absorb intracellular fluid and experience oncotic swelling, producing holes in the tight junctions

connecting the endothelial cells and creating the blood-brain barrier, which allows protein-rich fluid to flow into the brain extracellular space paracellularly (i.e., vasogenic edema). In the case of proceeding with the mechanisms, the oncotic/necrotic death of endothelial cells eventually results in losing capillary wall integrity (i.e., capillary fragmentation). The subsequent microvascular failure makes blood extravasated from the capillaries, creating petechial hemorrhages which can ultimately coalesce, enabling primary hemorrhage to expand (26, 32). PSH arises in a postponed manner, which is among its most distinguishing features. Furthermore, Sp1 and NF-B nuclear translocation, Abcc8 translation, transcription into SUR1 protein, and subsequent transfer to the cell membrane for many hours are regarded for creating SUR1-TRPM4 channels (31, 43). In an animal model of CNS injury and ischemia where the midbrain artery of a rat was blocked irreversibly, Abcc8 mRNA and SUR1 protein dropped by 2.5/3 and 2.5/8 hr/hr (43). Thus, there is a several-hour gap during which glibenclamide should be successfully given, blocking the opening of the SUR1-TRPM4 channel and preventing the development of edema and PSH. A variety of preclinical and clinical models was employed to evaluate this approach. Numerous studies have been performed in the TBI rat model to examine the effect of SUR1 and the effectiveness of glibenclamide on secondary trauma injury in the TBI animal models. The first study was related to 119 rats with a focal cortical contusion. After cerebral contusion, immunohistochemical, immunoblot, and in situ, hybridization analyses were carried out, the results of which revealed the overexpression of SUR1 significantly in the penumbral capillaries. A loading dose of glibenclamide (10 μg/kg) was treated to the intervention group within 10 min following the injury, supported by continuous drug infusion through a mini-osmotic pump. In the animals, small changes were observed in the contusion volume within the first 24 hours post-damage, while the volume doubled over the first 12 hr among those taking vehicles. After immunolabeling brain slices for vimentin, the capillaries of the mice receiving the vehicle were fragmented, while glibenclamide-given ones had normally-extended capillaries. Therefore, behavioral alterations were detected among the glibenclamide- and non-glibenclamide-treated rats (25, 32). Regarding CCI injury, some researchers assessed 68 adult Sprague–Dawley rats, administered a loading dose of glibenclamide (10 μg/kg) 15 min following the trauma, and proceeded with a 7-day continuous infusion to the intervention group. Compared to the vehicle-receiving animals, those given glibenclamide experienced a 15.3% decrease in the water content of brain tissue on the day post-trauma. Based on the results of the MRI examination, they had significantly less contusion at separate time points (1, 2, 3, and 7 days after trauma). However, the treatment failed to affect motor function seven days following the trauma according to the results of the beam-walking test (44, 45). Another study adopted an altered strategy to focus on the effect of glibenclamide on an improvement in post-TBI cognitive outcomes. TBI subjects commonly undergo a range of neurobehavioral symptoms and cognitive alterations, mostly for memory. The majority of the individuals first exhibited regular imaging, indicating that the kinetic energy conveyed by the TBI is inadequate to cause bleeding although it can originate neuronal damage. In this regard, a rat model was designed which simulates TBI cortical impact although it leads to a cortical contusion without bleeding in the hippocampus at the base. Additionally, the molecular changes separating the penumbra from the para-penumbra are recognized where there is synaptic damage and no hemorrhage, which was the hippocampus in this case. In the penumbra, both the NF-B and Sp1 transcription factors were active, and SUR1 increased in microvascular endothelial cells, making edema and PSH. Sp1 was alone triggered in the non-hemorrhagic para-penumbra neurons, in which the SUR1 expression elevated temporarily. The upregulation of SUR1 in para-penumbra neurons is associated with neuronal cell death mediated both by apoptosis and necrosis. However, glibenclamide stopped the process. At two weeks after injury, cleaved caspase-3 immunolabeling reduced among the ipsilateral brain of the rats treated with glibenclamide, and a decline was found in the Fluoro-Jade C staining in the contralateral hippocampus four-week post-injury (24, 25). The researchers used a Morris water maze to examine spatial memory for understanding do their data convert into variation in cognitive ability. All the rats under study had the same memory attraction and

retention following progressive learning, which can be achieved only by the neocortex. Further, the Morris water maze was applied to evaluate one-trial fast position learning (i.e., the capacity to find a new hidden platform site after just one learning trial), which required a perfect hippocampus one-month post-injury. The rats undergoing a placebo procedure, as well as those suffering from a cortical injury were treated with vehicle-based rats and overperformed with glibenclamide. Following its blockage of the SUR1-TRPM4 channel, glibenclamide may prevent neuronal degeneration along with PSH, and enhance cognitive outcomes after TBI. As for glibenclamide in human TBI, 33 subjects who received sulfonylurea at the time of an acute ischemic stroke and maintained the administration after hospitalization were compared with 28 control ones after treatment with oral diabetes other than sulfonylurea. Those receiving sulfonylureas had more probability to recover the national institutes of health stroke scale (NIHSS) score which decreased by four or more during admission to discharge. However, the intervention group had a more probability of having a positive result measured by a Rankin scale of less than or equal to two modified discharges (46). Kunte et al. (2012) evaluated 220 diabetes mellitus patients presenting with an acute ischemic stroke and maintained sulfonylurea for 43 individuals, while the other 177 were managed without the drug. Based on the results, 20 (11%) non-sulfonylurea-treated subjects experienced hemorrhagic transformation, while the value was zero in the sulfonylurea group (p=0.016). Furthermore, no individual died during the initial hospitalization in the sulfonylurea group although the mortality rate equaled 18 (10%) in another group (p = 0.027) (47). In another study, 32 diabetic patients who took and continued to take sulfonylurea at the time of TBI were compared to 38 diabetic ones receiving insulin. The sulfonylurea-given subjects were younger and possessed higher blood sugar levels although they had more inclination to meet the inputs of the Glasgow coma scale (GCS) (10 vs. 11). They spent significantly less time in the neuro-ICU (6 vs. 8 days). However, no significant variation was reported between the two groups in terms of GCS at discharge (13 vs. 13), GCS score at discharge (4 vs. 4), hospital duration (14 vs. 13 days), or PSH involvement (8/32 vs. 11/38 individuals). The positive GCS scores at admission and discharge, patients' ability to take medicines per os, and hospitalization duration indicated that the subjects did not suffer any serious injuries (47).

Conclusion

In conclusion, statin use in this retrospective cohort observational study of patients with TBI was not associated with beneficial or harmful effects on short- or long-term outcomes of TBI. Further evaluations are needed to more clearly determine whether statin use confers long-term benefits in patients with TBI.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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