A repurposed drug screen for regulating metabolic disease: an overview in the management of traumatic brain injury

Una detección de drogas reutilizada para regular la enfermedad metabólica: una descripción general en el manejo de la lesión cerebral traumática

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Abstract

Introduction & Background: The aim of this study is to review the mechanistic approaches and therapeutic opportunities in the management of traumatic brain injuries.

Methods: 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 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 up regulating endothelial nitric oxide synthase expression, enhancing neurogenesis and synaptogenesis, and anti-apoptotic effects, increased angiogenesis, and various antioxidant and anti-inflammatory mechanisms.

Results: Almost all studies have supported the potential role of statins in neuroprotection, and a few have mainly focused on their effects in traumatic brain injury models.ATP-sensitive potassium (KATP) channels are created, which can be demonstrated in pancreatic islet cells and certain neurons. 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.

Conclusion: 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 necessary procedure for industrial researchers and the scholarly community.

Keywords: Repurposed Drug, Mechanistic Approaches, Traumatic Brain Injury, statins, Sulfonylurea.

Resumen

Introducción y antecedentes. El objetivo de este estudio es revisar los enfoques mecanicistas y las oportunidades terapéuticas en el manejo de las lesiones cerebrales traumáticas.

Métodos. Se ha descubierto una gran cantidad de medicamentos reutilizados por casualidad en el laboratorio o mediante un seguimiento cuidadoso de la acción del fármaco en la clínica y el análisis retrospectivo de los hallazgos clínicos. Las estatinas se usan ampliamente para tratar la hiperlipidemia y prevenir enfermedades cardiovasculares, aunque su aplicación como agentes neuroprotectores que debilitan el daño neurológico secundario aún es limitada en la lesión cerebral traumática (TBI). Sus otros mecanismos de acción no mediados por el colesterol (es decir, pleiotrópicos) incluyen hasta regula la expresión de la sintasa de óxido nítrico endotelial, mejora la neurogénesis y la sinaptogénesis y los efectos antiapoptóticos, aumenta la angiogénesis y varios mecanismos antioxidantes y antiinflamatorios.

Resultados. Casi todos los estudios han respaldado el papel potencial de las estatinas en la neuroprotección, y algunos se han centrado principalmente en sus efectos en modelos de lesiones cerebrales traumáticas. Se crean canales de potasio sensibles al ATP (KATP), que se pueden demostrar en las células de los islotes pancreáticos y en ciertas neuronas. El receptor potencial transitorio de melastatina 4 (TRPM4) es la segunda subunidad formadora de poros de SUR1. Se ha observado la regulación positiva de SUR1 y la apertura de SUR1-TRPM4 en los diferentes modelos relacionados con lesiones del sistema nervioso central (SNC), como TBI. Las sulfonilureas pueden prevenir la degeneración neuronal y mejorar los resultados cognitivos posteriores a una TBI al inhibir el canal SUR1-TRPM4.

Conclusión. La reutilización de medicamentos, conocida como reposicionamiento de medicamentos, se considera un método para volver a desarrollar un compuesto para utilizarlo en una enfermedad específica, que ahora se está convirtiendo en un procedimiento cada vez más necesario para los investigadores industriales y la comunidad académica.

Palabras clave: Medicamento reutilizado, enfoques mecanicistas, lesión cerebral traumática, estatinas, sulfonilurea.

Introducción

Traumatic brain injury (TBI) is known as a major cause of morbidity and mortality worldwide, which is associated with the expenditure of huge resources on healthcare systems. The significance of this issue is more pronounced among the middle and low income countries, where risk factors for TBI are high, while healthcare systems are devoid of the facilities required to address relevant health outcomes[1]. TBI leads to functional deficiencies because of primary and secondary mechanisms. Primary damage is resulted from direct physical forces on the brain although it can irreversibly respond to prevent or reverse secondary brain damage. In addition, the brain injuries are created by the dynamic interactions among ischemic inflammatory cytotoxic processes. The hyper release of excitatory neurotransmitters (glutamic and aspartic acid), N-methyl d-aspartic acid, and amino-3-hydroxy-5 methyl 4-isoxazole propionic acid, as well as the potential-dependent hyper release of Ca^{2+} and Na^{+} channels is considered as the second stage of pathophysiological cascade. 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, lipid peroxidase (Px), as along with elevating the intracellular concentration of free fatty acids and radicals. Oxidative stress processes play a significant role in the pathogenesis related to secondary brain injury after occurring traumatic brain injury (TBI)[2]. The generation and release of free radicals following trauma is among the fundamental mechanisms leading to cytotoxicity, and subsequently organ failure, and excessive free radicals that overwhelm the body's antioxidant defenses. Many studies have used antioxidants like N-acetyl cysteine, vitamin C and E, and even iron chelators to combat post-traumatic oxidative stress, the results of which are inconsistent and unconvincing[3,4]. Despite significant strategies, none of 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[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) antagonist, 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 approach or elective treatments. The current study presents a brief outline of a few of such drugs.

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 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 up regulating endothelial nitric oxide synthase expression, enhancing neurogenesis and synaptogenesis, and anti-apoptotic effects, increased angiogenesis, and various antioxidant and anti-inflammatory mechanisms.

Statins have interesting pleiotropic properties such as antiapoptotic, antioxidative, and anti-inflammatory effects, which make them a suitable class of drugs for repurposing in TBI. No completely effective pharmacotherapies have been developed to improve the outcomes of traumatic brain injury (TBI). Given the reporting of cohort studies suggesting that preinjury statin use may reduce TBI-associated mortality, this study aimed to evaluate the effects of statin use in patients with TBI.

Inclusion criteria: Studies related to the effect of statins and their derivatives in the treatment of traumatic brain injury (TBI).

Exclusion criteria: Studies that were related to brain trauma, but in the process of their treatment, drugs other than statins and their derivatives were used were excluded from the study.

Overview:

Almost all studies have supported the potential role of statins in neuroprotection, and few have mainly focused on their effects in models of traumatic brain injury. ATP-sensitive potassium channels (KATP) can be expressed in pancreatic islet cells and certain neurons. Transient receptor potential melastatin 4 (TRPM4) is the second pore-forming subunit of SUR1. Upregulation of SUR1 and unfolding of SUR1-TRPM4 have been observed in various models of central nervous system (CNS) injuries such as TBI. Sulfonylureas may prevent neurodegeneration and improve cognitive outcomes after TBI by inhibiting the SUR1-TRPM4 channel.

Traumatic brain injury

TBI is a brain dysfunction caused by mechanical damage, which is one of the main causes of death and disability in people between 1 and 45 years old. The most common causes of TBI are falls, traffic accidents, assaults, and sports-related injuries [1]. According to the available data on the occurrence of this disease, the highest peak of this event is reported in teenagers, while the second peak is observed in the elderly. Incidence by gender shows that men are affected at least twice as often as women[2].

Atorvastatin and TBI

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 the 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 through 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-nonenal (4-HNE)[9,11]. 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 results in expressing prosurvival proteins like Bcl-2 and inhibit proapoptotic proteases such as caspase-3 from producing[12,13]. Based on the results of a study conducted on the primary cortical neuronal cultures related to E16–E17 fetal C57BL6 mice, simvastatin therapy improves Bcl-2 mRNA expression, and chronic treatment results in decreasing the activity of Aβ1–42-induced caspase 3 significantly. The preclinical studies in various animal models have revealed that the biochemical and genetic anti-apoptotic actions of statins can increase neuronal survival in TBI models and promote cognitive function[14]. 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 the animal models, post-traumatic treatment with 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 treating with atorvastatin at eight days after 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 is many of the strongest pathways for statin neuroprotection, which is less well-known. Stoll et al. (2005) claimed that statins prevent reactive oxygen species (ROS) production through 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 enzymeswith the above elevation in NOS expression[20,21]. In fact, they induce anti-inflammatory effects through reducing the formation of isoprenyl intermediates in the 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].

Based on the results, a significant reduction occurred in the expression of TLR4 and NFkappaB, inflammatory mediators such as tumour necrosis factor-alpha (TNF-), interleukin-1beta (IL-1), intracellular adhesion molecule-1, and interleukin-6 (IL-6), and (ICAM-1) compared to the control rats. Furthermore, treated rats had BBB impairment, motor defects, less cortical apoptosis, and brain oedema compared to the others.

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).

Table 1. Summary of Major Preclinical Studies Involving Statins

References	Drug	Dose	Experimental Model	Outcome Measure	Effect
Kureishi et al., [9]	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., [10]	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., [12]	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., [15]	Simvastatin and atorvastatin	1mg/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., [19] and Lu et al., [14]	Atorvastatin	1 mg/kg	Male Wistar rats, CCI	Histological evaluation of boundary zone, functional evaluation	Reduced functional deficits, increased neuronal su rvival and synaptogenesis in boundary zone, increased angiogenesis
Wang et al., [18]	Simvastatin and atorvastatin	20mg/kg	C57Bl /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., [16]	Simvastatin	1mg/kg	Male Wistar rats, CCI	VEGF and BDNF expression via ELISA	Elevated expression of BDNF and VEGF in the dentate gyrus
Chen et al., [17]	lovastatin	4mg/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., [22]	Simvastatin	37.5mg/kg	Adult male Wistar Rats weight-drop contusion	mRNA and protein expressions expressions of multiple inflammatory cytokines	Reduced expression of IL-1β, TNF, IL-6, ICAM-1
Lu et al., [14]	Lovastatin and simvastatin	10-9-10-5 M	Human BBB- derived endothelial cells	Diffusion rates Of bovine serum albumin and sucrose. across human BBB- ECs	50-60% reduction in the diffusion rates, significantly restricts the migration of multiple sclerosis-derived monocytes and lymphocytes across the human BBB in vitro

Progressive secondary hemorrhage following trauma, as well as 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[26]. 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[31]. The process was once considered to be created by the microvessels characterized at the time of injury leading to persistent bleeding, particularly with respect to 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 pathway, 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[31-33]. 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 the 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[34,35]. 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 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 to be extravasated from the capillaries, creating petechial hemorrhages which can ultimately coalesce, enabling primary hemorrhage to expand[26]. PSH arises in a postponed manner, which is among its most distinguishing features. Furthermore, Sp1 and NF-B nuclear translocation, Abcc8 translation and transcription into SUR1 protein, and subsequent transfer to the cell membrane for many hours are regarded for creating SUR1-TRPM4 channels[25,36]. 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 effectiveness of glibenclamide on secondary trauma injury in the TBI animal models. The first study was related to 119 rats with 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-hour post-damage, while the volume was doubled over the first 12 hr among those taking vehicles. After immunolabeling brain slices for vimentin, the capillaries of the mice receiving 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, and administered a loading dose of glibenclamide (10 μg/kg) 15 min following the trauma, 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-day post-trauma. Based on the results of MRI examination, they had a 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 beam-walking test[37,38]. 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 origin 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 penumbra from parapenumbra are recognized where there is synaptic damage and no hemorrhage, which was 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 nonhemorrhagic parapenumbra neurons, in which the SUR1 expression elevated temporarily. The upregulation of SUR1 in parapenumbra neurons is associated with the 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 same memory attraction and retention following progressive learning, which can be achieved only by 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 which were treated with vehicle-based rats 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 treating with an oral diabetes other than sulfonylurea. Those receiving sulfonylureas had more probability to recover the national institutes of health stroke scale (NIHSS) score of whom 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 discharge[39]. 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 ones 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 mortality rate equaled 18 (10%) in another group (p = 0.027)[40]. 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 level although they had more inclination to meet the inputs of 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 [40].

Effects of statin use in patients with TBI

Typically, after TBI a large amount of cytokines and chemokines will be released and an acute inflammatory response occurs in the central nervous system that can exacerbate the damage caused by TBI[41]. Theoretically, limiting neuroinflammation after head trauma can lead to reduced mortality and disability, which support the promising potential benefit of anti-inflammatory agents in treatment of patients with TBI[42,43]. There is a growing body of evidence that confirms the anti-inflammatory properties of statins, besides their cholesterol-lowering effect[44-46]. Statins can increase neurogenesis, suppress apoptosis, reduce microglial activity and ultimately reduce inflammation-induced astroglial activation[47,48].

Conclusions

The preclinical research represented that statins exhibit a range of cholesterol and non-cholesterol-mediated pharmacodynamic effects. The mechanisms include the upregulation of eNOS expression, as well as anti-apoptotic actions, higher angiogenesis, several antioxidant and anti-inflammatory pathways, and more neurogenesis and synaptogenesis. Many of the reviewed studies have revealed the possible contribution of statins to neuroprotection, and a few ones have compared the effect of statin in TBI models. As already mentioned, numerous preclinical studies on seemingly-promising neuroprotective drugs had difficulty in translating their effectiveness in the actual clinical examinations of TBI. During the last decade, our knowledge of secondary injury along with different CNS insults such as TBI has changed the characterization of the SUR1-TRPM4 channel. The opening and upregulation and of the channel are joined to edema formation, microvascular failure, PSH, as well as non-hemorrhagic neuronal death. In addition, SUR1 is considered as a valid target for pharmacological modulation since these processes lead to widespread damage and death in the CNS. Glibenclamide blocks channel opening at low doses, and efficiently reduces secondary damage after cortical impact without inducing hypoglycemia based on the animal model studies.

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Authors' Contributions
KB and YHA designed study conception; KB nad MSH conducted the literature search; KB, MM and MR interpretation of the data; KB Wrote the manuscript in consultation with YHA and MM; All authors read and approved the final form of manuscript.

Conflict of interest
The authors declare that they have no conflict of interests.

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