Journal of Pharmacopuncture

ISSN 2093-6966 [Print], ISSN 2234-6856 [Online]
Journal of Pharmacopuncture 2018;21[4]:226-240
DOI: https://doi.org/10.3831/KPI.2018.21.026

Review article

Neuroprotective Agents in the Intensive Care Unit
-Neuroprotective Agents in ICU -

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Key Words
neuroprotection, intensive care unit, stroke

Abstract

Neuroprotection or prevention of neuronal loss is a complicated molecular process that is mediated by various cellular pathways. Use of different pharmacological agents as neuroprotectants has been reported especially in the last decades. These neuroprotective agents act through inhibition of inflammatory processes and apoptosis, attenuation of oxidative stress and reduction of free radicals. Control of this injurious molecular process is essential to the reduction of neuronal injuries and is associated with improved functional outcomes and recovery of the patients admitted to the intensive care unit. This study reviews neuroprotective agents and their mechanisms of action against central nervous system damages.

1. Introduction

Neuroprotection aims at preventing neuronal loss and neurodegeneration through applying different agents to inhibit pathophysiological pathways that are injurious to the nervous system [1]. Use of neuroprotective agents has a long history from ancient Greece to the current age with the presence of pharmacological and natural neuroprotectants and gene therapies [1]. The most common conditions associated with nervous system involvement and Intensive Care Unit (ICU) admission are Trauma, shock, stroke, sepsis, traumatic brain injury (TBI) and ruptured brain aneurysm [1, 2].

2. Stroke

Stroke is one of the major causes of disability and death in the world [3]. Only one-third of patients with stroke recover enough to be free of disability [4]. Males have a greater incidence of stroke than females; hypertension, diabetes, atrial fibrillation, smoking and oral contraception pills are the major risk factors for stroke [2]. After stroke, decreased blood flow and subsequent disturbance in ionic homeostasis and intracellular edema are major consequences. Release of excitatory neurotransmitters and production of free radicals because of mitochondrial dysfunction occur consequently [5]. Oxidative stress, activation of apoptotic pathways and excitotoxicity are the subsequent events

Received: Dec 21, 2017 **Reviewed:** Aug 09, 2018 **Accepted:** Nov 14, 2018

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after cerebral ischemia that lead to neuronal death [4, 5].

3. Shock

Shock is defined as a decrease in blood perfusion to the body tissues and consequent deficiency in oxygen and substrate due to tissues and cell injuries [6]. Main types of shock include cardiogenic, hypovolemic, anaphylactic, septic and neurogenic shock [7]. Cellular ischemia is the primary cause of cell damage. After a decrease in blood perfusion to the cells, aerobic generation of ATP will decrease and mitochondrial dysfunction, increased intracellular PH, production of free radicals and autolytic pathway activation are following findings [6, 7].

4. Sepsis

Sepsis is a fatal condition with a high mortality rate [8]. Severe sepsis can lead to hypoperfusion and subsequent increase in serum creatinine level, an increase of serum lactate and total bilirubin level, thrombocytopenia and acute lung injuries [9]. Pneumonia, urinary tract infection and intra-abdominal infections are the most common causes of sepsis [10]. The incidence of Gram-negative bacterial infections have increased during the past decade [11]. The proinflammatory and anti-inflammatory responses are implicated in the tissue damage and secondary bacterial infection but specific responses depend on the host immune system and the causative pathogen [10, 11].

5. Traumatic brain injury

Trauma is one of the primary causes of disability and death worldwide [12]. TBI occurs as a result of sudden trauma to the head and leads to cognition, motor function and sensation impairment with a high mortality rate [13]. Increase in intracranial pressure, focal contusion, hematoma and cerebral edema formation occurs after trauma to the head [14]. The secondary part of TBIs will occur in cellular stage with severe consequences that have been described by Park and colleagues (2008) as; "*(1) failure of neuronal energy, (2) glial injury and dysfunction, (3) inflammation, (4) destruction and stenosis of microvasculature, (5) excitotoxicity (6) and aberrant ionic homeostasis in neurons"* [15].

6. Ruptured Brain Aneurysm

A brain aneurysm or a cerebral aneurysm is dilation of a supplied blood artery of the brain [16]. An unruptured aneurysm is often asymptomatic and recognizable by computed tomography or magnetic resonance imaging. The consequence of a ruptured brain aneurysm is subarachnoid hemorrhage that is a life-threatening condition [16]. Most of the brain aneurysms are congenital or with the familial background and genetic predisposition [17].

7. Mechanisms of neuronal injuries

Programmed cell dead (PCD), particularly apoptosis, excitotoxicity, oxidative stress, and inflammation are the primary mechanisms leading to neuronal injuries in the patients admitted to ICU [18]. PCD is a mixture of pathways that result in removal of the unwanted cell [19]. Several proteins such as caspases, apoptosis-inducing factor, Bcl-2 family proteins, p53 protein, tumor necrosis factor receptor, TRADD, Fas ligand and Fas-associated protein with death domain (FADD) are essential in the activation or inhibition of PCD pathways [19]. Three major routes have been defined for PCD that include intrinsic, extrinsic and caspase-independent pathways [20].

Some of the Bcl-2 family proteins have a significant role in the initiation of PCD by increasing mitochondrial permeability, the release of cytochrome-c from mitochondria and activation of caspases, known as the intrinsic pathway of apoptosis[21]. The extrinsic pathway works through triggering caspases-8 via membrane receptors like Fas and tumor necrosis factor-α [19, 20]. The release of apoptosis-inducing factor from mitochondria can induce apoptosis through a caspase-independent pathway [20].

Excitotoxicity is a primary mechanism of neuronal damage [22]. Glutamatergic neurons play an important role in the excitotoxicity [23]. As described by Dong et al. (2009), *"glutamate can activate N-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5methylisoxazole-4-propionate (AMPA) and kainic acid (KA) receptors"* [22]. Overactivation of glutamate receptors can lead to continuous activation of these receptors [24]. This constant activation results in: 1) cellular calcium hemostasis impairments [25], 2) oxidative stress and increased production of nitric oxide [26, 27], 3) generation of free radicals such as peroxynitrite and hydroxyl radical [28], and 4) PCD. Oxidative stress is associated with the accumulation of reactive species of nitrogen and oxygen (ROS) in the cell that leads to ATP depletion, mitochondrial dysfunction and impairment of cellular hemostasis [29]. Free radicals such as hydroxyl are highly active and can pair with DNA and lead to oxidation of DNA and cell death [29]. Oxidative stress and production of free radicals result in the activation of PCD [30]. In the ischemic neuronal injuries, the presence of inflammatory cytokines, leukocytes, and chemokines play a significant role in the pathogenesis of cell death [31, 32]. Cerebral blood flow occlusion leads to inflammatory reactions [33]. The presence of leukocytes and inflammatory mediators increase the level of adhesion proteins such as P-Selectin, E-Selectin and ICAM-1 results in the obstruction of microvessels, edema, necrosis and infarction [32, 33].

8. Neuroprotective agents

Beneficial use of many agents has been reported in the prevention of neuronal cell death in animal models but supportive data from clinical trials is still lacking [34]. New drugs have been introduced during the last decade with better outcomes in patients. We discuss some potent neuroprotective agents that may be beneficial for patients ad-

mitted to the ICU (Table 1).

8.1. Glutamate blockers

Glutamate is a neurotrasmitter and as described by Danysz et al. (2002), "it activates three major types of iono tropic receptors, namelyo~-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainateand N-methyl-D-aspartate (NMDA) and several types of metabotropic receptors. AMPA receptors are involved in fast glutamatergic neurotransmission" [35]. The major role of glutamate blockers are inhibition of glutamate binding to NMDA and AMPA receptors to avoid excitotoxicity [36].

Glutamate blockers such as polyarginine R18 and NA-1 (TAT-NR2B9c) were used in different studies in stroke models in rats [37, 38], non-human primates [39] and also in human [40]. Milani and colleagues reported R18 as a potential neuroprotective agent. In both studies on rat administration of R18 in 60 minutes post-stroke reduced infarct volume and cerebral edema, improved functional outcome, more efficient than NA-1 [37, 38]. These agents have Anti-excitotoxicity properties with inhibition of post-synaptic density-95 protein/nNOS complex [41]. Reduce of oxidative stress of mitochondria in neurons [42], reduction of calcium influx due to glutamate excitotoxic [43], proteolytic activity inhibition of proprotein convertases [44], are mechanisms of action for this class of neuroprotective agents.

8.2. Magnesium sulfate

Magnesium is the second abundant cation in the body. It is involved in different physiological pathways and has different clinical applications [45-47]. Magnesium activates the enzymatic process for the transfer of phosphate from ADP to ATP. It regulates intracellular calcium availability, cell cycle and mitochondrial function. Decrease of serum magnesium levels lead to hypocalcemia and hypokalemia. Magnesium also blocks NMDA receptor and leads to analgesia and neuroprotection [48].

Magnesium sulfate (MgSO4) is another potentiate neuroprotective agent with anti-excitotoxicity activity, blockage of N-methyl-D-aspartate (NMDA) channels and voltage-gated calcium channels inhibition properties [49, 50].

Use of MgSO4 have been documented in acute stroke [51-60], aneurysmal subarachnoid hemorrhage [61-68], and Traumatic brain injuries [49, 50, 69]. Monitoring of magnesium is vital for patients admitted to the ICU because low serum magnesium level is associated with high

Table 1 Potential neuroprotective agent in the intensive care unit for the management of hemorrhagic stroke, ischemic stroke and traumatic brain injuries.

References/Study	Neuroprotective Agent	Class	Clinical use	Recommended Dosage	Study population	Outcome
[37, 38]	polyarginine R18 NA-1 (TAT-NR2B9c)	Glutamate blockers	Ischemic Stroke	1000 nmol/kg	Rat	Reduced Infarct volume, cerebral swelling and functional outcomes
[50, 51, 58, 59, 61-68]	Magnesium sulfate (MgSO4)	Glutamate blockers / NMDA channels blocker	Hemorrhagic and ischemic Stroke, Traumatic brain injuries	Up to 65 mmol/day	Human Patients	MgSO4 reduced delayed cerebral ischemia and showed better outcome.
[93, 95, 96, 98]	Atorvastatin, Mevastatin, Rosuvastatin and Simvastatin	Statins	Ischemic Stroke	Up to 20 mg/kg/day	Mice and Human Patients	Good functional outcome, reduce of infarct size, increase of cerebral blood flow, lower mortality
[109-113, 223, 224]	Melatonin	Hormone	Hemorrhagic and ischemic Stroke, Traumatic brain injuries	Up to 200 mg/kg/day	New Zealand white rabbit, mice and rats	Prevention of vasospasm and apoptosis of endothelial cells, reduce oxidative damage
[119-123]	Erythropoietin	Hematopoietic growth factor	Hemorrhagic and ischemic Stroke, Traumatic brain injuries	Up to 5000 unit/Kg	Rabbit, Rat, Mice	Reduced infarct size, Attenuate vasospasm, good functional outcome

References/Study	Neuroprotective Agent	Class	Clinical use	Recommended Dosage	Study population	Outcome
[128-134]	NXY-059, PEG-SOD, Tempol, hydroxystilbene oxyresveratrol	Free Radical Scavengers	Ischemic Stroke, Traumatic brain injuries	2270 mg for initial infusion (NXY-059)	Rat and Human Patients	Improve of primary outcome, Improve cognitive outcome, (NXY-059) Other agents was not effective. NXY-059 was ineffective in a study [133]
[137, 139, 141]	Cyclosporin A (CsA) and FK506 (Tacrolimus)	Immunosuppressant	Ischemic Stroke, Traumatic brain injuries	Up to 10 mg/kg for CsA Up to 6 mg/kg for FK506	Rat	Reduction of infarct volume, improved functional recovery
[149, 153-155]	NAC	Mucolytic agent	Ischemic Stroke, Traumatic brain injuries	Up to 100 mg/kg, 600 mg twice daily (human patient)	Rat, Gerbil and A human Patients	Decrease of cerebral vasospasm, inhibition of apoptosis of the endothelial cells, Improve functional outcome
[158-164]	Esmolol, propranolol, labetalol, metoprolol, atenolol or carvedilol	Blockers of beta-adrenergic receptors	Traumatic brain injuries	10 mg/kg (Rat)	Rat, Human	Lower mortality rate, reduce of infarct volume
[170-172]	Flavocoxid, NS-398, Valdecoxib, Celecoxib	COX-2 inhibitors	Hemorrhagic and ischemic Stroke	Up to 200mg/kg/day (Flavocoxid), 20 mg/kg (NS-398), Up to 20 mg/kg twice daily (valdecoxib), 20 mg/kg/day (Celecoxib)	Rat, rabbit, mice	reduce of infarct volume and inhibition of neuro-inflammatory processes
[206-209]	Curcumin	Herbal medicine	Hemorrhagic and ischemic Stroke, Traumatic brain injuries	Up to 300 mg/kg	Mice	Attenuate of neurological deficit, Decrease of cerebral water content

mortality rate in the ICU [70, 71]. The use of MgSO4 in patients admitted to ICU has been associated with a decrease in the biomarkers such as S100B protein and serum neuron-specific enolase level (S-NSE) [72, 73].

8.3. Statins

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are the most frequntly administered class of cholesterol-lowering drugs [74] that have established effects in reducing coronary plaque volume [75] and cardiovascular events [76]. Beyond their well-known hypocholesterolemic effect, a myriad of lipid-independent pleiotropic activities have been described for statins [77-88]. Statins need to enter the cells, some of them are lipophilic and some are hydrophilic. Statins have different intestinal absorption after oral administration, differing from 30% (lovastatin) to 98% (fluvastatin). Systemic bioavailability of these drugs are 5-30%. Most of them are metabolized by cytochromeP-450 and have high protein binding [89].

Statins have antioxidant and anti-inflammatory actions [90-94]. Beneficial effects of atorvastatin, mevastatin, rosuvastatin and simvastatin in acute ischemic injuries have been reported in human patients as well as in animal models [95-98]. Mechanism of statins' actions include: (1) endothelial type III nitric oxide synthase (eNOS) up-regulation leads to inhibition of platelet activation; (2) reduce of malondialdehyde (MDA) and oxidized LDL (oxLDL); (3) alteration in the gene expression of inflammatory molecules such as VCAM-1, ICAM-1, E-selectin and interleukins [92, 93, 95].

As previously described, statins used for acute ischemic injuries with a different outcome. Some of these agents have better penetration into the cells, and it is because of the various lipophilic properties of this agents [99]. The use of statins has been reported with an increase in the risk of symptomatic hemorrhagic transformation (SHT) because of antithrombotic and fibrinolytic properties of these drugs [100, 101].

8.4. Melatonin

Melatonin or N-acetyl-5-methoxytryptamine is a neurohormone produced in the pineal gland that regulates circadian rhythm and has several clinical application[102]. Melatonin has low bioavalability (up to 56%) that is different from person to person. The plasma half-life is 20 to 50 minutes. Melatonin is metabolized by liver to at least 14 metabolites [103, 104]. Melatonin is the agonist of melatonin receptor 1 (MT1), melatonin receptor 2 (MT2) and nuclear receptor ROR-β [104, 105]. MT1 and MT2 are expressed in CNS and other body organs [105]. Expression of these receptors in the CNS leads to the regulation of central circadian rhythmicity [104]. Potential properties of melatonin like antioxidant effect, free radical scavenger, and anti-inflammatory reported in several studies [106-113].

Melatonin's mechanisms of action as neuroprotective agents are as below:

1) alteration of antioxidant enzymes gene expressions like catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) [114].
2) attenuation of the activation of Nuclear Factor- Kappa B (NF-κB) and activator protein 1 (AP-1); downregulation of tumor necrosis factor alpha (TNFα), Cyclooxygenase2 (COX2), Interleukin 1β [102, 111].
3) decrease in the level of phospho-Jun N-terminal Kinase 1 (p-JNK1) leads to suppression of apoptotic factors [102].
4) direct detoxification of free radicals like hydroxyl and protection of the DNA by donation of the electron [115].

Melatonin showed good outcome as neuroprotective agents in various neuropathologies [106-113].

8.5. Erythropoietin

Erythropoietin is a cytokine and hormone that is produced by the kidneys and the liver. It can stimulate erythropoiesis [116] and maitains the blood hemoglobin concentration under different circumstances [117]. Erythropoietin has a bioavailability of 20-30% after subcutaneous administration. Plasma half-life of this drug is more than 24 hours. Elimination half-life is up to 13 hours after intravenous administration [118]. Erythropoietin is indicated for the treatment of anemia because of various etiologies such as chronic kidney disease, chemotherapy, blood loss and drug adverse events [117].

The role of erythropoietin as a neuroprotective agent is documented in some studies on animal models [119-123]. Expression of erythropoietin receptor (EpoR) in the brain tissue is responsible for the neuroprotective effect of this agent [121]. Neuroprotective action of erythropoietin occurs through three signaling pathways and leads to inhibition of apoptosis [124].

Erythropoietin readily crosses the blood-brain barrier (BBB) after brain insult and even through normal BBB by specific receptors [119, 123]. It activates (1) Janus tyrosine kinase 2 (JAK-2)-STAT signaling pathways that lead to the expression of Bcl-2 [125, 126], (2) extracellular-regulated kinase (ERK) and Protein kinase B (PKB), (3) nuclear factor-kappa B (NF-κB) [123, 124]. Recently, carbamylated erythropoietin has been reported as a neuroprotective agent that acts via the CD131/GDNF/AKT pathway in mice [126]. It does not bind to EPO-R and does not stimulate erythropoiesis nor activates JAK-2 pathways [127].

8.6. Free Radical Scavengers

Free radical scavengers such as polyethylene glycol (PEG)-conjugated SOD (PEG-SOD), 4-hydroxy- 2,2,6,6-tetramethylpiperidine-1-oxyl (Tempol), trans-2,3',4, 5'-tetrahydroxystilbene (hydroxystilbene oxyresveratrol) and disodium 2,4-disulfophenyl-N-tert-butylnitrone (NXY-059) have been used as neuroprotectants in various animal studies [128-133]. PEG-SOD, tempol, and hydroxystilbene oxyresveratrol did not show significant effects on neuropathologies [129, 130, 134]. NXY-059 as a scavenger of reactive oxygen species (ROS) has been used in rats and humans [128, 132, 133], and has been shown to exert an-

tioxidant effects and vascular protective properties [128]. NXY-059 has been shown to be effective in the prevention of the salicylate oxidation [135]. Effectiveness of this drug is due to the entrapment of free radicals [135]. Around 80-90% of NXY-059 is eliminated unchanged through renal route. The elimination half-life is 2-4 hours in patients with normal kidney function [136].

8.7. Immunosuppressant drugs

Immunosuppressant drugs such as cyclosporine A (CsA) and particulaly tacrolimus (FK506) are recognized as neuroprotective agents in ischemic brain injuries and have been widely used in animal models [137-141]. Both cyclosporine and tacrolimus are calcineurin inhibitors. These agents bind to immunophilins and block the clacineurin that leads to reduced interleukin 2 production and T cells [142]. Tacrolimus is also a macrolid antibiotic and has more potency than cyclosporin with a different mode of immuphilin receptor inhibition [142]. Both drugs are substrate for cytochrome P450 3A4 and have potential renal and hepatic side effects [143].

One of the neuroprotective mechanisms of is blockage of extracellular signal-regulated kinases 1 and 2 (ERK1/2) [144]. ERK1 and 2 have pro-apoptotic properties and expression of these molecules occurs following the ischemic state [144]. FK506 inhibits calcineurin activity and nitric oxide (NO) production [140, 144]. Another mechanism of FK506 action is a reduction in the level of tumor necrosis factor-alpha (TNF-α) and IL-1beta [141] but it did not show anti-caspase-3 activity [145].

8.8. N-acetyl-L-cysteine (NAC)

NAC is an antidote for paracetamol toxicity and a thiol-containing drug with antioxidant, anti-inflammatory and free radical scavenging activity [146]. It is a safe medication with direct effects on glutathione synthesis. The main indication of NAC is in chronic bronchitis with hypersecretion of mucus, cystic fibrosis, acute respiratory distress syndrome and pulmonary oxygen toxicity. It can also attenuate brain oxidative stress. Infusion of NAC leads to the presence of the drug by up to 6 hours in plasma [146, 147].

Mechanisms of action of NAC as a neuroprotective agent are as below:

1) Increases the level of glutathione in the cells to prevent oxidative stress [146].
2) Inhibition of Nitric oxide synthase (NOS) and increases tissue oxygenation [148, 149].
3) Scavenging of the superoxide anions and ROS [149, 150].
4) Inhibition of endothelial apoptosis and NF-κB, TNF-α activation [151, 152].

NAC can cross BBB, depending on the route of administration and the dosage of the drug [148]. The decrease of cerebral vasospasm is reported in a human patients and animal models with Subarachnoid hemorrhage after administration of NAC [148, 153, 154]. The beneficial effect of NAC has been reported in acute ischemic and hemorrhagic stroke and TBI in rodents [149, 152-155].

8.9. β-Blockers

Beta-blockers are a class of drugs that are widely used to reduce blood pressure and control cardiac arrhythmias through blockage of β-adrenergic receptors. [156]. Beta blockers are water- and fat-soluble. Water-soluble β-blockers have longer half lives and have renal elimination while fat-soluble ones have shorter half lives and are metabolized by the liver. This class of drugs have a good absorbtion via oral route. These drugs reduce cardiovascular morbidity and mortality and induce vasodilation through nitric oxide and receptor blockage [157].

The benefit of beta-blockers in TBI has been investigated in animal models and human patients [158-164]. Mechanisms of action of beta-blockers as neuroprotective agents are inhibition of apoptosis, attenuation of TNF-α and interleukin-1β expression and improvement the cortical microvascular perfusion [158].

8.10. COX-2 selective inhibitors

COX-2 selective inhibitors are blocking agents of the cyclooxygenase-2 enzyme, and are classified as a member of nonsteroidal anti-inflammatory drugs. COX-2 stimulates inflammation by converting arachidonic acid to prostaglandin [165] and activating NMDA receptors [166]. COX-2 has a significant excitotoxicity role through overproduction of prostaglandins[167].

All COX-2 inhibitors are metabolized by cytochrome P450 enzymes. They are used for the treatment of osteoarthritis, rheumatoid arthritis and painful conditions. These drugs have a lower risk of developing gastrointestinal side effects compared with non-selective COX inhibitors. COX-2 inhibitors have also protective activity against neurodegenerative diseases [168, 169].

Several animal studies have been performed on the effect of various COX-2 inhibitors such as valdecoxib, celecoxib, some natural products and NS-398 [170-172]. The use of COX-2 antagonists was associated with an increase in glutathione and superoxide dismutase levels, reduction in the levels of TNF-α, IL-1β and NF-κB [170], and blockage of NMDA receptors [167].

8.11. Curcumin

Curcumin is a natural polyphenolic compound with numerous medicinal properties [173]. Curcumin is a hydrophobic product with poor oral absorption and bioavailability. Commercial curcumin known as curcuminoids is composed of curcumin, demethoxycurcumin and bisdemethoxycurcumin [174]. Curcumin has two keto and enol tautomeric forms that affect the stability of the molecule [175].

Curcumin has anti-inflammatory [176-180], antioxidant [178, 181-185], immunomodulatory [186-189], anti-tumor and chemo-sensitizing [190-196], analgesic [197], lipid-modifying [198-202] and hepatoprotective [203-205]

activities. Curcumin has been used for the treatment of TBI, ischemic and hemorrhagic stroke in animal models [206-209]. Various mechanisms have been suggested for the neuroprotective effects of curcumin. Zhu and colleagues reported that curcumin is an anti-inflammatory via *"inhibition of Toll-like receptor 4 (TLR4) / Myeloid differentiation primary response gene 88 (MyD88) / NF-κB signaling pathway"* [206] in TBI. Curcumin can inhibit inflammatory processes in hemorrhagic strokes by a reduction in the expression of matrix metalloproteinases (MMPs), attenuation of IL-1 and inhibition of p38 mitogen-activated protein kinases (p38MAPK)/protein kinase C (PKC) pathways [207, 208]. Another mechanism of curcumin's action in ischemic brain injuries is alteration of protein kinase B (Akt)/nuclear factorerythroid 2-related factor 2 (Nrf2) and reduction of oxidative damage [209].

Other neuroprotective agents such as corticosteroids [210, 211], barbiturates [212], ketamine [213], citicoline

Table 2 Other potential neuroprotectants in the intensive care unit.

References/Study	Neuroprotective Agent	Clinical use	Mechanism of action
[210, 211]	corticosteroids	Subarachnoid hemorrhage, ischemic stroke	Blocking of NF-kB, inhibiton of COX-2, expression of Mitogen-activated protein kinase phosphatase I
[212]	barbiturates	Intracranial aneurysm	Reduction of intracranial pressure, Supression of Cerebral metabolism
[213]	ketamine	Intracranial aneurysm	Inhibition of NMDA receptors
[214, 215]	citicoline	Stroke and TBI	Increase activity of glutathione reductase, lipid peroxidation attenuation, increase of sirtuin 1 expression
[216-219]	growth factors	Stroke and TBI	Inhibition in calcium incease, antiapoptosis, free radical scavengers
[220, 221]	minocycline	Stroke and TBI	Supression of IL-1β, IL-6 and TNF-α, Supression of MMP activity
[222, 225]	mannitol	Stroke and TBI	Free radical scavenger, Improve of brain microcirculation

COX-2: Cyclooxygenase-2

IL-1β: Interleukin-1β

IL-6: Interleukin-6

MMP: Matrix metallopeptidase

NF-kB: Nuclear factor-κB

NMDA: N-methyl-D-aspartate receptor

TBI : Traumatic Brain Injuries

TNF-α: Tumor Necrotic factor α

[214, 215], growth factors [216-219], minocycline [220, 221] and mannitol [222] with their mechanisms of action are summarized in Table 2.

9. Conclusion

Neurological complications continue to be a major problem in patients admitted to ICU and significantly affect clinical outcomes as well as the length of ICU stay. Over the decades and centuries, numerous neuroprotective agents have been introduced to improve the care of critically ill patients. Despite the usefulness of these agents, none of them was really effective in the management of patients admitted to the ICU. The beneficial impact of various neuroprotective agents has been shown in animal models. Inhibition of damaging signaling pathways to the neurons such as inflammation, oxidative stress and apoptosis is the major molecular mechanism of neuroprotective agents. Use of neuroprotective agents in the ICU should be supported by compelling evidence on the improvement of clinical outcome and rapid recovery in the patients. However, the efficacy of agents discussed above is controversial in the light of findings of clinical trials. Some clinical trials have shown favorable clinical outcomes after the use of magnesium in patients with stroke. Melatonin and erythropoietin may be regarded as effective neuroprotective agents with anti-inflammatory and anti-apoptotic properties. Further studies in large populations of ICU patients should be performed to evaluate the neuroprotective effects of various agents such as curcumin, erythropoietin, magnesium and melatonin.

Conflict of interest

The authors declare that there are no conflicts of interest.

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