Neuroprotective Agents: A Simple Overview

Andy Nugroho* and Ageng Sunjoyo

Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Universitas Sebelas Maret, Dr. Moewardi Hospital, Surakarta, Indonesia

Abstract

Neuroprotective agents are medications that can alter the course of metabolic events and have neuroprotective function. Neuroprotective agents are needed in patients undergoing a surgical procedure and clinical conditions that correspond with the central nervous system (CNS); also, in intensive care, the neuroprotective agents are often used to prevent complications and patient deterioration. Over the years, there is still no clear understanding of the potential for neuroprotection and the interactions between various drugs that serve a crucial role in anesthetic care and critical illness. This literature review will discuss further the mechanism of neuronal damage and various neuroprotective agents.

Introduction

“Neuroprotection” is defined as a collection of processes and strategies protecting neural tissues from cellular incidents (such as apoptosis, degeneration, and inflammation) associated with chronic neurodegenerative diseases (e.g., Parkinson’s disease, Alzheimer’s disease, and multiple sclerosis) as well as those derived from acute disorders (e.g., ischemia, stroke, or trauma) [1]. Neuroprotective agent is medications that can alter the course of metabolic events and have neuroprotective function. Neuroprotective agents are needed in patients undergoing the surgical procedure (cardiopulmonary bypass, carotid surgery, and cerebral aneurysm surgery) and clinical condition (subarachnoid hemorrhage, stroke, brain trauma, and post-cardiac arrest resuscitation) that correspond with the CNS, also in an intensive care unit (ICU), the neuroprotective agents often used to prevent complications and patient deterioration [2].

Since 2002

Clinical Conditions That Need Neuroprotective Agents

Stroke

Stroke is a primary reason that explains disabilities and mortalities on a global scale [3]. Excitatory neurotransmitters discharge and free radicals generation may occur due to post-stroke mitochondrial dysfunction. Oxidative distress, apoptotic pathway activation, and excitotoxicity subsequently emerge after cerebral ischemia, promoting neuronal death [4].

Shock

A major portion of cell damage is caused by cellular ischemia. After a cellular blood perfusion decrease, consecutively aerobic ATP creation declines, mitochondria experience dysfunction, intracellular pH rises, and free radicals are generated. These incidences are then followed by autolytic pathway activation that will cause neuronal damage [2].
Sepsis
Hypoperfusion and subsequent rise of serum creatinine levels, serum lactate increase, total bilirubin levels elevation, thrombocytopenia, and acute lung injury are possible effects of severe sepsis. Sepsis can cause cell damage and result in neuronal damage [5].

Traumatic brain injury (TBI)
The secondary portion of TBI will cause damage at the cellular stage with severe consequences including the following: (1) inflammation, (2) excitotoxicity, (3) failure of nerve energy generation, (4) glial injury and dysfunction, (5) microvascular destruction and stenosis, and (6) aberrant ionic homeostasis in neurons [6].

Pathophysiology of Neuronal Damage
Pathophysiological case of neuron damage
Energy formation failure
The brain is constantly supplied with oxygen and glucose. When this process is disrupted, the mitochondrial electron transport chain will be inhibited and oxidative phosphorylation. This will be followed within 1–2 min by decreasing the high-energy phosphate (phosphocreatine) level. Occurring structural damage will be permanent within 5–15 min during an oxygen-deprived environment, while hypoglycemia tolerance will be 60 min [4].

Tissue acidosis
Early minutes of cerebral ischemia witness a shift in the brain’s metabolic processes from aerobic respiration to anaerobic, which swiftly generates lactic acid and acidifies brain pH from 6.5 until 6.7. Hyperglycemia exacerbates this mechanism, dropping tissue pH further to 6.0. Due to the N-methyl-D-aspartate (NMDA) receptors blockage, acidosis may have a neuroprotective effect [4].

Membrane depolarization and cerebral edema
Energy-dependent membrane ions may become dysfunctional as a primordial result of ATP deprivation which allows Na⁺ and Ca²⁺ entry into the cell and the exit of K⁺. Highly concentrated intracellular Na⁺ and Ca²⁺ enables a Cl⁻ and H₂O influx into neurons, causing cytotoxic edema and sequentially increasing intracranial pressure (ICP) [4].

Intracellular Ca²⁺ excess
Lack of ATP will lead to a colossal Ca²⁺ excess surge into the cell and presynaptic excitatory amino acids reuptake failure. Both processes boost the excitotoxic neurotransmitter glutamate accumulation in the extracellular space, resulting in an excitotoxic cellular wound. Phospholipases A1, A2, and AC are subsequently activated, therefore, hydrolyzing phospholipids in mitochondria and cell membranes and generating free fatty acids (e.g., arachidonic acid). The remnants of these processes can then be catabolized into free radicals, prostaglandins, and leukotrienes, which alter membrane permeability and ion distribution [4].

Mitochondrial damage
In mitochondria, oxidative phosphorylation is supposed to produce ATP through glucose oxidation continuously. Ischemic or traumatic disorders disrupt oxygen and glucose delivery and impair mitochondrial function, causing ATP production to be inadequate. As a key event leading to mitochondrial injury, an abnormal surge of Ca²⁺ in the cells either activates degradative enzymes (e.g., calpain proteases and phospholipases) or enzymes responsible for building oxygenated free radicals. It is noteworthy that intracellular Ca²⁺ will enable permeability transition in a mitochondrial stage [4].

Peri-infarction depolarization
Energy failure causes electrochemical membrane depolarization and excitation of neurons and glial cells. This event produces a wave of depolarization that travels away from the nuclear lesion with a frequency of up to eight events per hour. As repolarization is an energy-dependent process, which further stresses metabolically impaired cells in the penumbra, peri-infarction depolarization and repolarization may contribute to lesion growth [4].

Free oxygen radicals
Free oxygen radicals are physiologically produced in small amounts in cellular processes such as oxidative phosphorylation in the mitochondrial electron transport system. Under normal conditions, the resulting superoxide radical undergoes a spontaneous dismutation of superoxide dismutase (SOD) to hydrogen peroxide, forming a hydroxyl radical. Hydroxyl radicals react with almost all intracellular molecules. Superoxide radicals can also react with nitric oxide (NO) to create highly reactive peroxynitrite radicals. Normal defense systems against free radical damage include enzymatic systems that scavenge or scavenge free radicals (e.g., SOD, catalase, glutathione peroxidase, and Vitamins E and C). During cerebral ischemia and reperfusion,
the concentration of superoxide and hydroxyl radicals increases rapidly, and the normal defense system is overwhelmed. Since radicals can react and damage almost all cellular components, this excess of free oxygen radicals further promotes cell disintegration [4].

**Neuroprotective Agent**

*Intravenous anesthesia agent*

**Thiopental**

Administration too quickly before the onset of circulatory failure can adversely affect it because it can interlink with diminishing energy stores and lead to hypotension, ischemia, or both. Thiopental and other barbiturates suppress electroencephalographic (EEG), thus subtracting the required amount of ATP. According to Schwer et al., recent studies exhibited evidence at the molecular level that thiopental prevents hypoxic neuronal death by decreasing the brain’s metabolic activities and its assembly of global protein, thereby assisting the energy balance maintenance in oxygen-deprived cells and nutrients [7].

**Propofol**

The mechanism of the post-conditioning impacts of propofol exerted post-cerebral ischemia or post-reperfusion injury results from incremented neuronal hypoxia tolerance, attenuated inflammatory reactions, or decreased apoptosis-induced stress endoplasmic reticulum [8].

**Ketamine**

Ketamine is a non-competitive N-methyl-D-aspartic acid (NMDA) receptor antagonist capable of post-ischemic nerve cell loss reduction by glutamate-induced excitotoxic injury prevention, which is executed through regulating apoptotic proteins and by interfering with the inflammatory response. Ketamine does not increase ICP [9].

**Etomidate**

Several preclinical pieces of research have shown etomidates’ neuroprotective effects through depressing brain metabolism, inhibiting post-ischemic hyperemia, and attenuating vascular-mediated inflammation. On the contrary, other studies discussed the etomidate capability of exacerbating the ischemic injury because it inhibits nitric oxide synthetase, which intensifies ischemic insult. Hence, its usage as a neuroprotective agent is quite frowned upon in clinical practice, while its neuroprotective efficacy remains unevaluated [10]. This imidazole derivative induces swiftly with minimal cardiac function or respiratory rate changes and acts in a short duration [7].

**COX-2 selective inhibitor**

COX-2 selective inhibitors inhibit the cyclooxygenase-2 enzyme. COX-2 converts arachidonic acid to prostaglandins and activates NMDA receptors, stimulating inflammation. It is shown that they protect against neurodegenerative diseases as well. Research on animals has been conducted on various COX-2 inhibitors. COX-2 antagonists usage is associated with increased levels of glutathione and superoxide dismutase, decreased levels of TNF-α, IL-1β, and NF-κB, and blockage of NMDA receptors [11].

**Immunosuppressant agents**

Cyclosporine A (CsA) and particulate tacrolimus (FK506) are known as immunosuppressant drugs with neuroprotective qualities against ischemia-related brain injuries. As calcineurin inhibitors, both medications bind to immunophilin and block calcineurin, leading to decreased interleukin 2 and T cell production. Tacrolimus is well-known as a macrolide antibiotic and bears higher potency than cyclosporine, differently from the inhibition of the immunophilin receptor, even though both drugs are substrates for cytochrome P450 3A4 and notorious for their potential side effects on kidneys and liver. One of their neuroprotective mechanisms is blocking extracellular signal-regulated kinases 1 and 2 (ERK1/2), both bearing pro-apoptotic properties and expressed post-ischemia. FK506 inhibits calcineurin activities as well as nitric oxide (NO) construction. FK506 also acts in the mechanism of decreasing TNF-alpha and IL-1beta, even though it does not exhibit anti-caspase-3 activity [12].

**Beta-blocker**

As neuroprotective agents, beta-blockers act under a mechanism of action consisting of apoptosis inhibition, TNF- and interleukin-1β expressions attenuation, and increased cortical microvascular perfusion [13], [14].

**Nerinetide/NA-1**

Nerinetide, more commonly known as NA-1, protects neurons from excitotoxicity by interfering with the interaction between the scaffolding protein, PSD-95, with the NMDA receptor, thus preventing the receptors from signaling. ESCAPE-NA1 is the first Phase III, randomized, and controlled trial studying neuroprotective treatment in stroke patients contexted in endovascular thrombectomy. The primary outcome of
Stimulates and restores Na+/K+ as well as ATP activities, averts barbiturates bind to -aminobutyric acid type A receptors.

60–90 min
<1 min
30 s
1000 mg IV/day

Propofol can work by enabling GABA from GABA receptors in the brain while hindering neurotransmitters’ work within the brain.

Inhibits NF-kB and COX-2, as well as Mitogen-activated protein kinase phosphatase.

Hinders apoptosis, attenuates TNF-α and IL-1β expression and boosts cortical microvascular perfusion.

Hinders ATP levels loss

Changes in metabolic processes and bioenergy processes in neurons increase protein synthesis.

Lactate-related vasodilator, hyperosmotic and anti-edematous effect, thereby lowering intracranial pressure.

Hypertonic sodium lactate (HSL) is a promising hyperosmolar fluid that functions not only to lower ICP but also to provide exogenous lactate to meet the increased energy demands of the brain [18]. Hypertonic lactate solution reverses impaired brain metabolism and oxygenation after brain injury by reducing brain edema, increasing mitochondrial respiration, and reducing mitochondrial changes. Although clinical studies are still needed, hypertonic lactate solutions may be considered to maintain cerebral integrity in traumatic brain injury [19].

Giving sodium lactate and mannitol are equally effective in reducing intracranial pressure in patients with severe head injury. Administration of sodium lactate increased lactate levels significantly compared to administration of mannitol [20] (Table 1).

### Citicoline

Cytidine-5’-diphosphocholine (CDP-choline) is an endogenous compound that can increase neurotransmitters levels in the CNS by interacting with cellular membrane phospholipids synthesis, particularly phosphatidylcholine synthesis. It is more widely known as citicoline. Citicoline enables neuroprotection against Alzheimer’s disease, stroke, Parkinson’s disease, glaucoma, and amblyopia. Citicoline provides neuroprotective effects for patients with progressive glaucoma even though intraocular pressure is well controlled [16], [17].

### Piracetam

Piracetam is a drug called a “nootropic,” one of a class of drugs that affect mental function and is a neuroprotective agent. Healthy volunteers improved higher brain functions involved in cognitive processes, such as learning and memory. Its mechanism of action is unknown but may include increased cholinergic neurotransmission [17].

### Totilac/hypertonic sodium lactate

Hypertonic sodium lactate (HSL) is a promising hyperosmolar fluid that functions not only to lower ICP but also to provide exogenous lactate to meet the increased energy demands of the brain [18]. Hypertonic lactate solution reverses impaired brain metabolism and oxygenation after brain injury by reducing brain edema, increasing mitochondrial respiration, and reducing mitochondrial changes. Although clinical studies are still needed, hypertonic lactate solutions may be considered to maintain cerebral integrity in traumatic brain injury [19].

Giving sodium lactate and mannitol are equally effective in reducing intracranial pressure in patients with severe head injury. Administration of sodium lactate increased lactate levels significantly compared to administration of mannitol [20] (Table 1).

### Conclusion

Neurological complications preserve their role as a major problem in surgery and intensive care patients, significantly hampering patients’ clinical outcomes and lengthening their stay in the ICU. For level A evidence, we can choose Ketamine, Etomidate, and Citicoline for neuroprotective agents. The other agents might be useful as shown by level B evidence include Thiopental, Propofol, Beta-blockers, COX-2 selective inhibitor, Piracetam, and Totilac. Inhibiting deleterious pathways that signal to neurons (inflammation, oxidative stress, apoptosis, and those alike) are the main molecular mechanisms of neuroprotective agents. The use of neuroprotective agents should be supported by strong-evidenced improvements in clinical outcomes and patient’s speed of recovery.

### Acknowledgments

This study was supported by the Department of Anesthesiology and Intensive Therapy Faculty of Medicine Universitas Sebelas Maret, Dr Moewardi General Hospital Surakarta.
Author Contributions

The first author designed the study and analyses data. The second author collected data and wrote the manuscript. All authors read and approved the final version of the manuscript.

References

1. Fukuda S, Warner DS. Cerebral protection. BJA Br J Anaesth. 2007;99(1):10-7. https://doi.org/10.1093/bja/aem140 PMid:17573393

2. Panahi Y, Mojtahedzadeh M, Najafi A, Rajae SM, Torkaman M, Sahebkar A. Neuroprotective agents in the intensive care unit: Neuroprotective agents in ICU. J Pharmacopuncture. 2018;21(4):226-40. https://doi.org/10.3831/KPI.2018.21.026 PMid:30652049

3. Tahir RA, Pabaney AH. Therapeutic hypothermia and ischemic stroke. Altteratureview. SurgNeuroInt. 2016;?Suppl14:S381-6. https://doi.org/10.4103/2152-7806.183492 PMid:27313963

4. Engelhard K, Werner C. Mechanisms of neuronal injury and cerebral protection. In: Core Topics in Neuroanaesthesia and Neurointensive Care. United Kingdom: Cambridge University Press.; 2018. p. 33-44. https://doi.org/10.1017/cbo9780511977558.004

5. Chong J, Dumont T, Francis-Frank L, Balaan M. Sepsis and septic shock: A review. Crit Care Nurs Q. 2015;38(2):111-20. https://doi.org/10.1097/ncq.0000000000000052 PMid:25741952

6. Gruenbaum SE, Zlotnik A, Gruenbaum BF, Hersey D, Bilotta F. Pharmacologic neuroprotection for functional outcomes after traumatic brain injury: A systematic review of the clinical literature. CNS Drugs. 2016;30(9):791-806. https://doi.org/10.1007/S40263-016-0355-2 PMid:27339615

7. Chrousos GP, Katzung B, Trevor A. Basic and clinical pharmacology. In: Adrenocorticosteroids Adrenocortical Antagon 13th ed. New York: McGraw-Hill Medical.; 2015.

8. Mahajan C, Chouhan RS, Rath GP, Dash HH, Suri A, Chandra PS, et al. Effect of intraoperative brain protection with propofol on postoperative cognition in patients undergoing temporary clipping during intracranial aneurysm surgery. Neuror India. 2014;62(3):262-8. https://doi.org/10.4103/0028-3806.136908 PMid:25053847

9. Hudetz JA, Iqbal Z, Gandhi SD, Patterson KM, Byrne AJ, Hudetz AG, et al. Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery. Acta Anaesthesiol Scand. 2009;53(7):864-72. https://doi.org/10.1111/j.1399-6576.2009.01978.X PMid:19422355

10. Drummond JC, McKay LD, Cole DJ, Patel PM. The role of nitric oxide synthase inhibition in the adverse effects of etomidate in the setting of focal cerebral ischemia in rats. Anesth Analg. 2005;100(3):841-6. https://doi.org/10.1213/01.ANE.0000146519.85312.21 PMid:15728077

11. Singh DP, Chopra K. Flavocoxid, dual inhibitor of cyclooxygenase-2 and 5-lipoxygenase, exhibits neuroprotection in rat model of ischaemic stroke. Pharmacol Biochem Behav. 2014;120:33-42. https://doi.org/10.1016/J.PBB.2014.02.006 PMid:24561313

12. Mbye LH, Singh IN, Carrico KM, Saatman KE, Hall ED. Comparative neuroprotective effects of cyclosporin A and Nim811, a nonimmunosuppressive cyclosporin A analog, following traumatic brain injury. J Cereb Blood Flow Metab. 2009;29(1):87-97. https://doi.org/10.1038/JcbfM.2008.93 PMid:18714317

13. Khalili H, Ahl R, Paydar S, Sijolin G, Cao Y, Niakan A, et al. Beta-blocker therapy in severe traumatic brain injury: A prospective randomized controlled trial. World J Surg. 2020;44(8):1844-53. https://doi.org/10.1007/S00268-020-05391-8 PMid:32002583

14. Frishman WH, Saunders E. β-Adrenergic blockers. J Clin Hypertens (Greenwich). 2011;13(9):649-53. https://doi.org/10.1111/j.1751-7176.2011.00515.X PMid:21896144

15. Hill MD, Goyal M, Menon BK, Nogueira RG, Mctaggart RA, Demchuk AM, et al. Efficacy and safety of nimodipine for the treatment of acute ischaemic stroke (ESCAPE-NA1): A multicentre, double-blind, randomised controlled trial. Lancet. 2020;395(10227):878-87. https://doi.org/10.1016/S0140-6736(20)30258-0 PMid:32087818

16. Iulia C, Ruxandrea T, Costin LB, Liliana-Mary V. Citicoline-a neuroprotector with proven effects on glaucomatous disease. Rom J Ophthalmol. 2017;61(3):152-8. https://doi.org/10.22336/rjo.2017.29 PMid:29450391

17. Sokolova I, Tazina S, Zakharova O. Neuroprotective therapy with citicoline and piracetam at acute cerebrovascular disease: Clinical and psychosomatic effects. FABAD J Pharm Sci. 2021;46(3):299-310.

18. Arifianto MR, Ma’ruf AZ, Ibrahim A, Bajamal AH. Role of hypertonic sodium lactate in traumatic brain injury management. Asian J Neurosurg. 2018;13(4):971-5. https://doi.org/10.4103/ajns.ajns_10_17 PMid:30459851

19. Millet A, Cuisinier A, Bouzat P, Batandier C, Lemasson B, Stupar V, et al. Impact of a selective cyclooxygenase-2 inhibitor, celecoxib, on cortical excitability and electrophysiological properties of the brain in healthy volunteers: A randomized, double-blind, placebo-controlled study. PLoS One. 2019;14(2):e0212689. https://doi.org/10.1371/journal.pone.0212689 PMid:30794658