



Neuroprotective Agents: A Simple Overview

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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.

Edited by: Mirko Spiroski
Citation: Nugroho A, Sunjoyo A. Neuroprotective Agents: A Simple Overview. Open Access Maced J Med Sci. 2022 Sep 02; 10(F):578-582. <https://doi.org/10.3889/oamjms.2022.10329>
Keywords: Anaesthetic care; Critical illness; ICU; Neuroprotection; Neuroprotective agent
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Received: 04-Jun-2022
Revised: 18-Aug-2022
Accepted: 25-Aug-2022
Copyright: © 2022 Andy Nugroho, Ageng Sunjoyo
Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist
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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].

Over decades, studies have been conducted on anesthetic and non-anesthetic drugs to seek the possibility of neuroprotective qualities. However, there is no clear understanding of the potential for neuroprotection and the interactions between various drugs that play an important role in anesthetic care and critical illness. Thus, this becomes the objective for writing a literature review, which will discuss further

the mechanism of neuronal damage and various neuroprotective agents.

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 Ca^{2+} entry into the cell and the exit of K^+ . Highly concentrated intracellular Na^+ and Ca^{2+} enables a Cl^- and H_2O influx into neurons, causing cytotoxic edema and sequentially increasing intracranial pressure (ICP) [4].

Intracellular Ca^{2+} excess

Lack of ATP will lead to a colossal Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} 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 inducts 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-, IL-1 β , and NF- κ B, 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-1 β 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

Table 1: Summary of neuroprotective agents

Agent Name	Dose	Onset	Ways of working	Level of Evidence	References
Thiopental	Loading dose 3–6 mg/kg	30 s	Barbiturates bind to γ -aminobutyric acid type A receptors.	B	[7]
Propofol	1 mg/kg/min	<1 min	Propofol can work by enabling GABA from GABA receptors in the brain while hindering neurotransmitters' work within the brain.	B	[8]
Ketamine	Loading dose 1–2 mg/kg	10–15 min	Ketamine blocks the N-methyl-D-aspartate channel.	A	[9]
Etomidate	Loading dose 0.2–0.5 mg/kg	1 min	Etomidate conceals the systems used for reticent activation and mimicking GABA effect on inhibition	A	[7]
Immunosuppressant Agent (Cyclosporin A)	20 mg/kg/day	1.5–2 h	Inhibits NF- κ B and COX-2, as well as Mitogen-activated protein kinase phosphatase	C	[12]
Beta-Blockers	20 mg/day	60–90 min	Hinders apoptosis, attenuates TNF- α and IL-1 β expression and boosts cortical microvascular perfusion	B	[13], [14]
COX-2 Selective Inhibitor	400 mg/day	3 h	Increased levels of glutathione and superoxide dismutase	B	[11], [20]
Nerinetide	2–6 mg/kg/day	?	Interfere with the PSD-95 and NMDA interaction	B	[15]
Citicoline	1000 mg IV/day	60 min	Stimulates and restores Na ⁺ /K ⁺ as well as ATP activities, averts neuronal ATP levels loss	A	[16], [17]
Piracetam	4.5 g/day	30–90 min	Changes in metabolic processes and bioenergy processes in neurons increase protein synthesis.	B	[17]
Totilac	Intraoperative: 3mL/kg in 15 minutes iv followed by 1.5mL/kg/h Post-operative: 1mL/kg/h for 12 h iv	-	Lactate-related vasodilator, hyperosmotic and anti-edematous effect, thereby lowering intracranial pressure	B	[18], [19]

ATP: Adenosine triphosphate, COX: Cyclooxygenase, GABA: Gamma-aminobutyric acid, IL: Interleukin, NF- κ B: Nuclear factor- κ B, NMDA: N-methyl-D-aspartate, PSD-95: Postsynaptic density protein 95, TNF: Tumor necrosis factor.

a trial finished in 2019 was a disability scores reduction in acute stroke patients with small infarct cores identified for sudden EVT (NCT02930018) [15].

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.

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