Clinical neuroprotection and secondary neuronal injury mechanisms

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Abstract

Multiple disease processes can ultimately lead to cerebral injury, a common cause of both severe morbidity and mortality in patients of all age groups. Cerebral injury is seen in a variety of both medical and surgical conditions, including stroke, subarachnoid haemorrhage, central nervous system infection, epilepsy, post cardiac arrest and, of course, traumatic brain injury.

Although the primary damage to brain tissue may be irreversible, aggressive early physiological, pharmacological and surgical interventions may limit the ensuing secondary brain injury caused by ongoing ischaemia, and reduce the risk of severe disability or death.

Keywords Cerebral protection; decompressive craniectomy; secondary brain injury; stroke; traumatic brain injury

Royal College of Anaesthetists CPD matrix: 1A01, 1A02, 2F01

Learning objectives

After reading this article you should be able to:

- outline the pathophysiology of secondary brain injury
- list mechanisms for physiological cerebroprotection
- list drugs used and their actions for pharmacological cerebroprotection.

Secondary brain injury

The cascade of events that ultimately results in cerebral cell death begins at the instant of primary brain injury. Following this there are both local and systemic insults that may act alone, or together to cause secondary brain injury (Box 1).

The most common factors leading to secondary brain injury are hypoxia and hypoperfusion, which result in cellular ischaemia, oedema formation, brain swelling, and disruption of the blood–brain barrier, thereby leading to an increase in intracranial pressure that further reduces cerebral perfusion setting up a vicious cycle of ischaemic insult.

Pathophysiology

Tissue ischaemia leads to the accumulation of lactic acid due to anaerobic glycolysis. As a consequence of the inefficient energy production due to anaerobic metabolism, the ATP stores deplete and the energy-dependent cellular membrane ion pumps fail. These intracellular events lead to increased membrane permeability and cellular and tissue oedema.[1]

The second stage of this pathophysiological cascade is characterised by terminal membrane depolarisation along with excessive release of excitatory neurotransmitters (glutamate and aspartate), activation of *N*-methyl-D-aspartate, α-amino-3-hydroxy-5-methyl-4-isoxazolpropionate, and voltage-dependent calcium (Ca^{2+}) and sodium (Na^{+}) channels. The consequent Ca^{2+} and Na^{+} influx, in turn, lead to catabolic intracellular processes. Ca^{2+} activates lipid peroxidases, proteases, and phospholipases that increase the intracellular concentration of free fatty acids and free radicals. These, along with activation of endonucleases, translocases and caspases lead to structural disintegration of cellular membranes and nucleosomal DNA causing DNA fragmentation and inhibition of DNA repair.

The final stage of the cascade is an increase in expression of genes determining programmed cell death leading to necrosis (apoptosis).

Different parts of the brain respond differently to the same insult with some areas being more vulnerable compared to others.

Cerebral neuroprotection

There are physiological, pharmaceutical and surgical measures that can be put in place to provide cerebral neuroprotection. Ideally these should be instituted before the onset of the ischaemic process as close to the onset of the primary brain insult as possible. Cerebral protection involves creating the most

Causes of secondary brain damage

Extracranial causes

- Hypoxia
- Hypotension
- Metabolic
  - Hyponatremia
  - Hyperthermia
  - Hypoglycemia/hyperglycaemia

Intracranial causes

- Haemorrhage
  - Extradural
  - Subdural
  - Intracerebral
  - Intraventricular
  - Subarachnoid
- Swelling
  - Venous congestion/hyperaemia
  - Oedema
- Vasogenic
- Cytotoxic
- Interstitial
- Infection
  - Meningitis
  - Brain abscess
- Infarction

Box 1

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favourable conditions possible for the brain to ensure optimal functioning as a long-term objective (Box 2).

Physiological strategies for neuroprotection

Control of hypoxaemia: hypoxaemia, defined as arterial oxygen tension (PaO_2) <8 kPa, is associated with a significant increase in mortality in patients with severe traumatic brain injury (TBI), defined as those patients with a Glasgow Coma Score (GCS) <8. A low brain tissue oxygen tension often indicates ongoing cerebral ischaemia. Aggressive correction of hypoxaemia is mandatory and may require early tracheal intubation and mechanical ventilation in the most severe of cases. Current guidelines suggest that a PaO_2 >13 kPa should be targeted.[2]

Blood pressure control: after an insult to the brain, autoregulation is diminished or lost; with the consequence that cerebral blood flow (CBF) becomes directly related to systemic mean arterial pressure. Even moderate hypotension (systolic blood pressure [SBP] <90 mmHg) is associated with a twofold increase in mortality in patients with TBI. Current guidelines recommend that while no specific number should be targeted, even a single episode of SBP <90 mmHg should be avoided. Hypotension should be managed with aggressive fluid resuscitation and, if necessary, vasoactive agents.[2]

Temperature control and hypothermia: in experimental models of brain injury, hypothermia has been shown to decrease the cerebral metabolic rate to a degree of 7% per degree Celsius fall in temperature. It not only slows metabolic processes but also immune and inflammatory responses to injury. Hypothermia also obtunds neurotransmitter release and therefore prevents apoptosis.

This process, however, has not been demonstrated clinically, and despite these findings, for most conditions there is no improvement in morbidity or mortality due to induced hypothermia. Induced hypothermia may also cause sepsis, coagulopathies and arrhythmias, particularly in patients with existing risk factors for these conditions. It is therefore not routinely recommended in the majority of cases.[3]

Cerebral protection strategies

Physiological

- Blood pressure control
- Maintenance of oxygenation
- Arterial carbon dioxide control
- Temperature control
- Glycaemic control

Pharmacological

- Propofol
- Thiopental
- Benzodiazepines
- Volatile anaesthetic agents
- Hyperosmolar agents
- Nimodipine
- Magnesium

Surgical

- Decompressive craniectomy

Box 2

There is a role for hypothermia, however, in comatose patients following 'return of spontaneous circulation' post cardiac arrest, and current guidelines recommend an induction of a mild hypothermia (32–34 °C) for 12–24 hours post cardiac arrest followed by a controlled rewarming.

Glycaemic control: there is a direct and proven relationship between hyperglycaemia and poor outcome after brain injury. By the same adage, hypoglycaemia is also detrimental to neurological recovery, so insulin-induced hypoglycaemia must be avoided. For the purposes of neuroprotection, reasonable control of blood glucose levels (≤10 mmol/litre) should be maintained at all times.

Seizures: seizures compromise the oxygen and substrate supply to the brain. They may be difficult to detect in comatose patients and the only sign could be failure to recover from neuromuscular blockade after surgery or prolonged sedation and ventilation. As seizures can be inconspicuous, yet vital in depleting the brain tissue of resources, early recognition through clinical examination and investigation such as an electroencephalogram (EEG), along with early treatment is important (see Pharmacological strategies).

Hypercapnia and hypocapnia: it is recognised that in hypercapnic patients, a 1 kPa change in arterial carbon dioxide ($PaCO_2$) increases CBF by 25–35%.[1] Conversely, in hypocapnia a 1 kPa change in $PaCO_2$ decreases CBF by 15%. There are maximal effects to the changes in CBF above 10–11 kPa and below 2.5 kPa.[4,5]

Hyperventilation to achieve hypocapnia in patients used to be popular when treating brain injury. However, while the response to changes in $PaCO_2$ is prompt, with a half life of 20 seconds, this response is not sustained long term, wearing off after between 6 and 12 hours of hypocapnia. There is also evidence that excessive hyperventilation may worsen perfusion to some ischaemic areas of the brain following a TBI. Current guidelines suggest that $PaCO_2$ is maintained between 4.5 and 5 kPa and although hyperventilation may be considered in cases of severe brain injury, blood flow and oxygen delivery to the brain must be monitored closely during this intervention.

Pharmacological strategies for neuroprotection

Thiopental reduces the cerebral metabolic rate and cerebral blood flow and is also an anti-epileptic drug.

Historically, this drug has been frequently used to manage TBI; however, dosing needs to be closely monitored due to the hypotensive effects of this agent, and indeed, there is no clear evidence that it confers improved neurological outcome. Due to its principal side effect of hypotension and its tissue accumulation (terminal half life of 11 hours), it is now not favoured as a first-line sedative agent, and is only considered as a second-line agent when all other strategies have failed.

Propofol offers neuroprotection as both cerebral metabolic rate and CBF are reduced in a dose-dependent manner with use of this agent, such that an isoelectric EEG may be achieved. Epileptiform movements have been observed with its use but there is no evidence to suggest that these are due to cortical seizure activity or epilepsy. Propofol has a shorter half life than thiopental (terminal half life of 3–4 hours) and is therefore a favoured sedative agent. Prolonged infusions are associated with

propofol infusion syndrome so patients treated with long-term infusions of this agent (more than 48 hours and at doses greater than 5 mg/kg/h) should be monitored closely.

Benzodiazepines offer neuroprotection, but to a much lesser extent than propofol or thiopental. They also act by reducing CBF and cerebral metabolic rate. They have a place in co-induction, long-term sedation, and as anticonvulsants in the treatment of some cerebral diseases.

Volatile agents: all volatile agents lead to cerebral vasodilatation and also suppress cerebral metabolism. A balance between these two determines the final response. At lower concentrations they are similar to the intravenous agents and they offer neuroprotection by suppressing neuronal energy requirements, however, at higher levels, they increase the CBF due to vasodilatation. Sevoflurane has the least effect on CBF of all the currently available agents.

Hyperosmolar therapy: there are currently two osmotic agents commonly used for their effects on cerebral oedema and raised intracranial pressure (ICP).

Mannitol — decreases ICP by reducing blood viscosity, which in turn results in increased blood flow leading to vasoconstriction secondary to an increased oxygen delivery. In addition, it has also been shown to decrease the rate of cerebral spinal fluid (CSF) formation.

In the presence of an intact blood–brain barrier, mannitol draws out water from brain tissue into the plasma via osmosis; however, the agent should be used with caution, as in a non-intact blood–brain barrier the molecules may leak into the tissue themselves and cause tissue oedema through the same osmotic effect in the opposing direction.

Hypertonic saline — may be as effective as mannitol in reducing ICP. In studies comparing this agent to mannitol, it is not as efficacious in some conditions such as sub-arachnoid haemorrhage but has a role in TBI with a disrupted blood–brain barrier.[6,7]

Apart from acting as an osmotic agent like mannitol, it also causes endothelial cell dehydration thereby increasing the lumen of blood vessels and increasing cerebral perfusion.

It is also known to restore neuronal membrane potential and has an anti inflammatory effect on the neural cells.

Sodium bicarbonate: use of sodium bicarbonate to lower intracranial pressure is still under investigation but has shown promising results in the initial but small isolated studies. These studies have used 85 ml of 8.4% sodium bicarbonate instead of 100 ml hypertonic saline and have noted that a single dose of 8.4% sodium bicarbonate is as effective at treating rises in ICP for at least 6 hours without exposing patients to the risks of a hyperchloraemic metabolic acidosis.[8]

Nimodipine is a cerebro-selective calcium channel blocker used in the treatment of subarachnoid haemorrhage. It improves outcome by preventing vasospasm associated with subarachnoid haemorrahge and also by exerting neuroprotective effects. There is no evidence for a beneficial role of this drug in TBI.

Corticosteroids reduce cerebral oedema around brain tumours and are therefore commonly used for this condition; however, there is no evidence of them lowering ICP or improving outcome after TBI or stroke.

They are immunosuppressive and may cause hyperglycaemia unless closely monitored.

Magnesium is a calcium antagonist that can also antagonise NMDA receptors and glutamate release and has been shown to improve outcome after subarachnoid haemorrhage but can worsen outcome in TBI. Its only current routine use is in hypomagnesaemic patients.[9]

Surgical strategies for cerebroprotection-decompressive craniectomy

The aim of a decompressive craniectomy is to relieve the tension on the brain tissue enclosed in the cranial vault by removing part of the skull bone, thus giving brain tissue space to expand and therefore decreasing the ICP and improving cerebral perfusion.

While it is known to convert mortality following a middle cerebral artery brain infarct from 60% to 20% and to decrease mortality in TBI patients, the opinions on the benefits of this procedure are divided.

There is no doubt that the procedure improves survival in many patients who would otherwise die of a raised ICP that has failed to respond to other measures. However, it has been noted that many of these patients actually survive to have a poor quality of life after surgery (persistent vegetative state) and therefore one should question whether the results justify this treatment in all patients.[10] ◆

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