Clinical neuroprotection and secondary neuronal injury mechanisms

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Abstract

Cerebral injury is a common cause of severe morbidity and mortality and is frequently encountered by anaesthetists and intensive care physicians in clinical practice. Insults may arise from a variety of medical and surgical conditions, including stroke, subarachnoid haemorrhage, central nervous system infection, epilepsy, post-cardiac arrest, and traumatic brain injury (TBI).

Although the primary damage to brain tissue may be irreversible, aggressive early treatment may limit the ensuing secondary brain injury and reduce the risk of severe disability or death. Neuroprotection involves physiological, pharmacological and surgical interventions, initiated before the onset of ischaemia that can modify the cascade of events that lead to permanent cell damage when left unchecked.

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

Royal College of Anaesthetists CPD Matrix: 1A01, 2F01, 3F00

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 (Table 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. These in turn increase the intracranial pressure which further reduces cerebral perfusion setting up a vicious cycle of ischaemic insult.

Pathophysiology

At a cellular level, tissue ischaemia leads to the conversion from aerobic to anaerobic metabolism with a subsequent increase in lactate production. As a result 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]

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The second stage of this pathophysiological cascade is characterized by terminal membrane depolarization 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, leads 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 cause a 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 when compared to others.

Neuromonitoring

Neuromonitoring allows early detection of secondary events in critically ill patients with cerebral injury.

The overall aims of neuromonitoring are to:

- identify worsening neurological function and secondary cerebral insults that may benefit from specific treatment(s)

Causes of secondary brain damage

Extracranial causes	Intracranial causes
Hypoxia	Haemorrhage
Hypotension	• Extradural
Metabolic	• Subdural
• Hyponatraemia	• Intracerebral
• Hyperthermia	• Intraventricular
• Hypoglycaemia/ hyperglycaemia	• Subarachnoid
	Swelling
	• Venous congestion/ hyperaemia
	• Oedema
	Vasogenic
	Cytotoxic
	Interstitial
	Infection
	• Meningitis
	• Brain abscess
	Infarction

Table 1

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- improve pathophysiological understanding of cerebral disease in critical illness
- provide clear physiological data to guide and individualize therapy
- assist with prognostication.

Several techniques are now available for global and regional brain monitoring that provide early warning of impending brain ischaemia and allow optimization of cerebral haemodynamics and oxygenation (Box 1). Modern neurointensive care utilizes a combination of these monitoring techniques (multimodal monitoring) to identify or predict secondary cerebral insults and guide therapeutic interventions in order to maximize the potential for good outcome after brain injury. Developments in multimodal monitoring have allowed a movement away from rigid physiological target-setting towards an individually tailored, patient-specific approach.[2]

Cerebral neuroprotection

The treatment goal after cerebral injury, both during the acute resuscitation phase and later in the intensive care unit, is to prevent and treat cerebral ischaemia in order to minimize the degree of secondary cerebral damage and maximize the potential for neurological recovery. Interventions to achieve this goal may be divided into physiological, pharmacological and surgical treatments. Cerebral protection involves creating the most 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 (PaO_2 < 8 kPa) is associated with a significant increase in mortality in patients with severe traumatic brain injury (TBI) (i.e. those with a Glasgow Coma Scale score <8) and low local 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 greater than 13 kPa should be targeted.[3]

Blood pressure and cerebral perfusion pressure control: the level of systolic blood pressure (SBP) plays a critical role in the secondary injury cascade.

There are several underlying pathophysiologic mechanisms. If autoregulation remains intact, a drop in SBP triggers an autoregulatory vasodilation in an attempt to maintain adequate brain perfusion. This results in increased cerebral blood volume, which in turn elevates intracranial pressure. If autoregulation is not intact, there is dependency on SBP to prevent cerebral ischaemia.

The traditional definition of hypotension has been an SBP less than 90 mmHg, and this was the target recommended in previous guidelines. However, current literature now supports maintaining SBP at a higher level that may vary by age (i.e. SBP at ≥100 mmHg for patients 50–69 years old or at ≥110 mmHg or above for patients 15–49 or over 70 years old).[3] This is achieved by appropriate volume resuscitation and, if required, inotropic support, which should be titrated using invasive blood pressure monitoring.

Cerebral perfusion pressure (CPP) is the difference between the mean arterial blood pressure and intracranial pressure (ICP). Views on the optimal CPP have evolved over the years. Recent years have seen increased attention to patients' pressure autoregulatory status with the view that patients with intact autoregulation are best served by higher CPP values while pressure-passive patients with dysfunctional pressure autoregulation do

Monitoring techniques

Intracranial pressure monitoring
- Intraventricular catheter
- Microtransducer system
- Fibreoptic devices

Cerebral blood flow
- Transcranial Doppler ultrasonography
- Thermal diffusion flowmetry – continuous

Cerebral autoregulation
- Pressure reactivity index

Cerebral oxygenation
- Positron emission tomography
- Jugular venous oxygen saturation
- Brain tissue oxygenation
- Near infrared spectroscopy

Cerebral microdialysis
- Glucose
- Lactate—pyruvate ratio
- Glycerol
- Glutamate

Continuous electroencephalography

Multimodal monitoring

Box 1

Cerebral protection strategies

Physiological
- Maintenance of oxygenation
- Blood pressure control
- Temperature control
- Glycaemic control
- Seizure management
- Arterial carbon dioxide control
- Haemoglobin management

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

Surgical
- Decompressive craniectomy
- Drainage of cerebrospinal fluid – external ventricular drainage

Box 2

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