Therapeutic hypothermia and acute brain injury

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Abstract

The neuroprotective effects of therapeutic hypothermia (TH) have been recognized for decades, but these have generally failed to translate these into improved outcome in clinical studies. Here, we provide an overview of the putative mechanisms of hypothermia-induced neuroprotection, the technical considerations for the clinician wishing to use TH, and review the evidence for the clinical application of TH after acute brain injury (ABI).

Although TH is increasingly used as a tool in the management of intracranial hypertension, its role in different ABI types is not yet fully established. Many questions remain regarding the logistics of cooling (including length of treatment), and how best to manage complications of therapy, particularly shivering. The only level I evidence for its benefit lies in adult cardiac arrest and neonatal hypoxic-ischaemic encephalopathy. Further high-quality studies are needed to assess the role of TH in other ABI types.

Keywords Acute ischaemic stroke; hypoxic-ischaemic encephalopathy; intracerebral haemorrhage; intracranial pressure; subarachnoid haemorrhage; therapeutic hypothermia; traumatic brain injury

Royal College of Anaesthetists CPD matrix: 1H02, 2F01, 3F00

Learning objectives

After reading this article, you should be able to:

- understand the mechanisms of hypothermia-induced neuroprotection
- evaluate the role and evidence for therapeutic hypothermia after acute brain injury
- recognise the effect of hypothermia on intracranial pressure
- discuss the main complications associated with therapeutic hypothermia.

The neuroprotective effects of therapeutic hypothermia (TH) have been recognized for decades, but many preclinical studies have failed to translate these into effective clinical benefit. The aim of this article is to provide an overview of the putative mechanisms of hypothermia-induced neuroprotection, and present evidence about the use of TH in different forms of acute brain injury (ABI).

Physiological mechanisms of therapeutic hypothermia

Traditionally, hypothermia was believed to induce neuroprotection primarily as a consequence of reduced cerebral metabolic activity, decreasing the chance of cellular energy failure and subsequent cell death.[1] Preclinical studies, predominantly animal models of focal and global cerebral ischaemia intending to replicate acute ischaemic stroke and cardiac arrest, respectively, have revealed that hypothermia has a multifactorial action, exerting its influence on virtually all pathways that lead to cell death (Figure 1). These include apoptosis, inflammation, excitotoxicity, and free radical production.[2] Hypothermia has also been shown to affect cerebral blood flow (CBF) as well as metabolism, preserve integrity of the blood–brain barrier (BBB), and possibly influence tissue regeneration through neurogenesis, gliogenesis and angiogenesis.[2]

Stabilization of the BBB decreases the risk of cerebral oedema and rises in intracranial pressure (ICP). Indeed, reduction in ICP is the most robust clinical manifestation of hypothermia when body temperature is $\leq$35.5 °C.[1] Reductions in ICP associated with TH are also likely to be related to dampening of inflammatory responses and reduction in cerebral blood volume. The benefits of TH over other therapies in reducing ICP are several; it is more effective than several more traditional measures (Table 1), and it can reduce ICP refractory to these treatments.[3] It is for these reasons that moderate hypothermia is used in some centres as a generic intervention for intracranial hypertension.

Data illuminating the above mechanisms have overwhelmingly come from animal studies, but modern imaging and multimodality neuromonitoring techniques are now being harnessed in clinical studies of hypothermia to better understand the potential benefits in different ABI types.

Technical aspects of therapeutic hypothermia

The process of TH is typically separated into three distinct phases – induction, maintenance and rewarming. Cooling methods can be divided into those that cool the whole body and those targeted at the head alone. Intravascular or surface cooling techniques, with feedback loops to maintain a set temperature, are available and have been reviewed in detail elsewhere.[1] Rapid induction of hypothermia can be achieved with the application of ice packs and cold intravenous fluids.[1]

There are several important adverse effects associated with TH (Table 2), and close monitoring and management of shivering, blood glucose, electrolyte levels and fluid balance is essential. Localized head cooling reduces the risk of systemic complications of TH, but there is currently insufficient evidence to recommend its use outside the research setting.[4]

Rewarming is the most dangerous phase of TH, and rebound rises in ICP and hyperkalaemia are of particular importance (Table 2). Slow re-warming is mandatory and temperature increases of between 0.1 and 0.25 °C per hour have been recommended.[1]

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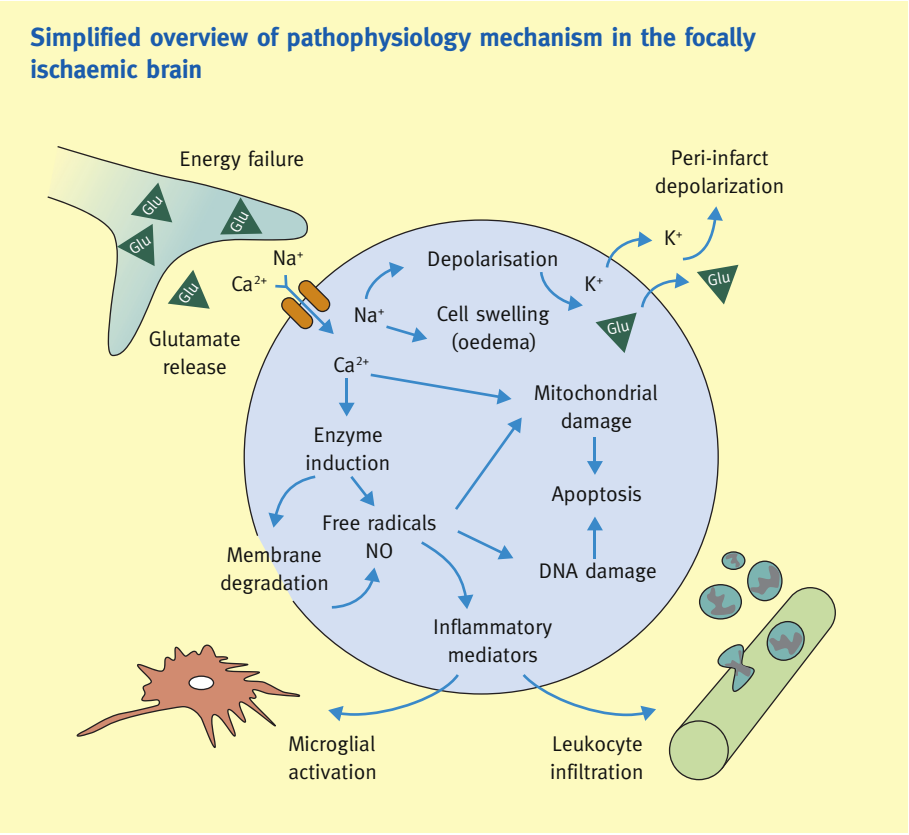

Figure 1 Energy failure leads to depolarization of neurones. Activation of specific glutamate receptors dramatically increases intracellular Ca^{2+}, Na^{+}, Cl^{-} levels, while K^{+} is released into the extracellular space. Diffusion of glutamate (Glu) and K^{+} in the extracellular space can propagate a series of spreading waves of depolarization (peri-infarct depolarizations). Water shifts to the intracellular space via osmotic gradients and cells swell (oedema). The universal intracellular messenger Ca^{2+} overactivates numerous enzyme systems (proteases, lipases, endonucleases, etc.). Free radicals are generated, which damage membranes (lipolysis), mitochondria and DNA, in turn triggering caspase-mediated cell death (apoptosis). Free radicals also induce the formation of inflammatory mediators, which activate microglia and lead to the invasion of blood-borne inflammatory cells (leukocyte infiltration) via upregulation of endothelial adhesion molecules. (Reproduced with permission from Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. *Trends Neurosci* 1999; **22**:391–7. With kind permission from Elsevier.)

Clinical applications of hypothermia in acute brain injury

Therapeutic hypothermia has been used in a variety of clinical conditions (Table 3).

Traumatic brain injury

Although multiple observational and phase II clinical trials identified potential outcome benefits from TH after traumatic brain injury (TBI), two phase III trials in adults (the National

Comparative effects of contemporary therapies for intracranial hypertension

Therapy	Total number of patients identified in reviewed studies	Average decrease in ICP	Standard deviation
Hyperventilation	126	6.08	4.22
Mannitol	140	7.93	5.34
Barbiturates	167	8.47	6.71
Hypothermia	367	9.97	6.66
Hypertonic saline	133	15.06	7.34
CSF drainage	72	15.45	4.67
Decompressive craniectomy	192	19.15	7.70

CSF, cerebrospinal fluid; ICP, intracranial pressure.

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Table 1