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Review

Neuroprotective hypothermia – Why keep your head cool during ischemia and reperfusion

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ABSTRACT

Background: Targeted temperature management (TTM) is the induced cooling of the entire body or specific organs to help prevent ischemia and reperfusion (I/R) injury, as may occur during major surgery, cardiac resuscitation, traumatic brain injury and stroke. Ischemia and reperfusion induce neuronal damage by mitochondrial dysfunction and oxidative injury, ER stress, neuronal excitotoxicity, and a neuroinflammatory response, which may lead to activation of apoptosis pathways.
Scope of review: The aim of the current review is to discuss TTM targets that convey neuroprotection and to identify potential novel pharmacological intervention strategies for the prevention of cerebral ischemia and reperfusion injury.
Major conclusions: TTM precludes I/R injury by reducing glutamate release and oxidative stress and inhibiting release of pro-inflammatory factors and thereby counteracts mitochondrial induced apoptosis, neuronal excitotoxicity, and neuroinflammation. Moreover, TTM promotes regulation of the unfolded protein response and induces SUMOylation and the production of cold shock proteins. These advantageous effects of TTM seem to depend on the clinical setting, as well as type and extent of the injury. Therefore, future aims should be to refine hypothermia management in order to optimize TTM utilization and to search for pharmacological agents mimicking the cellular effects of TTM.
General significance: Bundling knowledge about TTM in the experimental, translational and clinical setting may result in better approaches for diminishing I/R damage. While application of TTM in the clinical setting has some disadvantages, targeting its putative protective pathways may be useful to prevent I/R injury and reduce neurological complications.

1. Introduction

Ischemia and reperfusion (I/R) of the brain results in extensive neuronal injury and forms a substantial medical burden because of high morbidity and mortality. In adults, cerebral ischemic insults typically result from ischemic stroke or cardiac arrest, while in infants cerebral ischemia generally ensues from complications during labor and delivery or surgery for congenital heart disease, resulting in neonatal hypoxic-ischemic encephalopathy [26]. The high oxygen and glucose demands of the brain compared to other organs require continuous blood supply, which is guaranteed under physiological conditions by the autoregulation of brain circulation. However, the relatively high oxygen and glucose demand makes the brain extremely vulnerable to hypoxia and ischemia. Disrupted blood flow causes an imbalance between the energy generated by glucose oxidation, the main source for energy in the brain, resulting in loss of cellular homeostasis. Restoring blood flow and thus re-establishing nutrient and oxygen delivery to the ischemic brain is essential to salvage neurons, although reperfusion itself causes additional, substantial brain damage [56]. Reperfusion injury occurs due to enhanced production of reactive oxygen species in mitochondria, disruption of calcium (Ca^{2+}) homeostasis through glutamate-induced excitotoxicity, an exaggerated neuroinflammatory response by stimulation of the TNF-receptor, and a cellular stress response in the endoplasmic reticulum (ER), which may further damage neuronal cells [50].

Targeted temperature management (TTM) is thus far generally applied in aforementioned conditions as a neuroprotective strategy to prevent acute ischemia-reperfusion injury (I/R injury) of the central nervous system (CNS). TTM is the induced cooling of the body or a specific organ to prevent or treat injuries. The impact of TTM seems to depend on the target temperature [66]. Randomized studies directly comparing different target temperatures are often performed by comparing just two temperature targets [13,45]. However, protection by TTM is highly dependent on the clinical setting, as well as type and

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extent of the injury. Clinical application of TTM encompasses a wide spectrum of neurological conditions and complications. Mild (32–35 °C) and moderate hypothermia (28–32 °C) prevent further injury during or following cardiac arrest [23], hypoxic-ischemic encephalopathy in neonates [58], traumatic brain injury [72], and may be used to prevent brain injury during or after stroke. Deep hypothermia (<28 °C) on the other hand is used during circulatory arrest in surgical procedures on congenital heart disease in neonates, aortic arch in adults, and intracranial aneurysms [37]. Although current data suggest that TTM protects against I/R neuronal injury, the precise underlying mechanisms remain to be elucidated. Revealing the molecular mechanisms of TTM in neuronal I/R (Fig. 1) may allow to identify potential targets and assist the development of novel pharmacological intervention strategies against cerebral I/R injury. In this review, we give an overview of the molecular mechanisms underlying neuronal I/R-induced cell death, neuroprotective effects of TTM in I/R injury and possible pharmacological approaches to mimic TTM.

2. Cerebral ischemia leads to mitochondrial dysfunction and oxidative injury

I/R injury is characterized by mitochondrial dysfunction and oxidative stress in the brain. The acute decrease in cerebral oxygen and glucose levels during ischemia lead to an imbalance in energy homeostasis, which disrupts mitochondrial function. Disruption of mitochondrial function leads to reduced adenosine triphosphate (ATP) production, impaired Ca^{2+} buffering by opening of the mitochondrial permeability transition pore (mPTP) and, in particular, the overproduction of reactive oxygen species (ROS) as found in in vitro cardiomyocytes [32] and in the brain [14]. In certain situations, such as mitochondrial Ca^{2+} overload induced by *N*-methyl-D-aspartate (NMDA) receptor overstimulation, cellular stability relies primarily upon energy production, i.e. mitochondrial function [57]. High intracellular Ca^{2+} levels damage the mitochondria by activating the Ca^{2+} sensitive protease calpain, which then cleaves mitofusin2 (MFN2), leading to mitochondrial fragmentation [64]. As fragmentation of the mitochondrial network proceeds, it results in further neuronal damage because of progressive ATP depletion. The enhanced Ca^{2+} uptake into the mitochondria, combined with the increase in metabolic rate provoked by increased intracellular Ca^{2+}, results in the formation of ROS [52,57].

Increased intracellular Ca^{2+} levels ultimately also increase the Ca^{2+} in mitochondria, which triggers ROS production. ROS radicals will react with virtually any cellular component, such as carbohydrates, amino acids, DNA and phospholipids. Free radicals furthermore trigger a vicious cycle in the mitochondria, with inhibition of electron transport mechanisms leading to excess superoxide production and activation of apoptotic mechanisms. During cerebral ischemia complexes I, II, and III of the mitochondrial respiratory chain are damaged, leading to impaired electron transport and excess superoxide production [43]. ROS production is closely linked to excitotoxicity, energy loss and ionic imbalances. The CNS is a particularly vulnerable to ROS-mediated injury because it only holds moderate levels of endogenous antioxidants and antioxidant enzymes and these levels decrease rapidly following I/R injury. ROS induce a pro-apoptotic state in which generation of the Bcl-2 family members Bax/Bak permeabilize the mitochondrial membranes by creating large pores. Mitochondrial membrane permeabilization is a critical factor in determining the survival of neuronal cells. The permeabilization is initialized to counteract the effect of high intracellular Ca^{2+} levels have on mitochondrial Ca^{2+} homeostasis. Permeabilization of the mitochondrial outer membrane (MOM) results in the release of pro-apoptotic proteins from the intermembrane space to the cytoplasm, including cytochrome c, which can lead to apoptotic cell death [25]. Also, MOM permeabilization decreases mitochondrial ATP generation by disturbing the mitochondrial membrane potential ($\Delta\Psi$) and thereby uncoupling the process of respiration from ATP synthase. The decrease in $\Delta\Psi$ and subsequent uncoupling results from the opening of the mitochondrial permeability transition pore (mPTP) in response to elevated levels of mPTP activators (Ca^{2+}, ROS, inorganic phosphate from used ATP) and decreased levels of mPTP inhibitors (ATP/

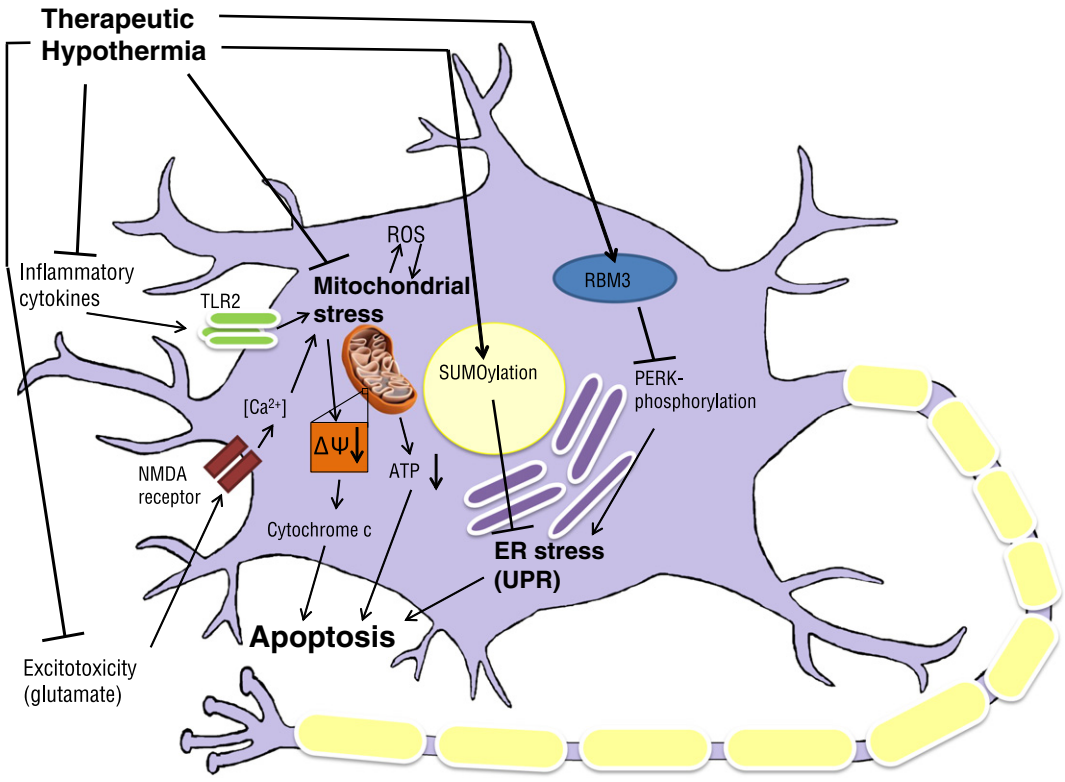

Fig. 1. Overview of protective properties of therapeutic hypothermia on molecular pathways in the neuron.