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Hypothermia and brain inflammation after cardiac arrest

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Abstract:

The cessation (ischemia) and restoration (reperfusion) of cerebral blood flow after cardiac arrest (CA) induce inflammatory processes that can result in additional brain injury. Therapeutic hypothermia (TH) has been proven as a brain protective strategy after CA. In this article, the underlying pathophysiology of ischemia-reperfusion brain injury with emphasis on the role of inflammatory mechanisms is reviewed. Potential targets for immunomodulatory treatments and relevant effects of TH are also discussed. Further studies are needed to delineate the complex pathophysiology and interactions among different components of immune response after CA and identify appropriate targets for clinical investigations.

Keywords:

Brain injury, cardiac arrest, inflammation, therapeutic hypothermia

Introduction

Despite major improvements in resuscitation, neurological injury after cardiac arrest (CA) has remained a major cause of morbidity and mortality among survivors.[1,2] Brain injury occurs not only during the CA ("no-flow" injury) and resuscitation ("partial-flow" injury) but also after reestablishment of brain reperfusion ("reperfusion" injury). Inflammatory processes after ischemia-reperfusion (I/R) induced by CA play a pivotal role in neurological damage. So far, no pharmacological treatment has been approved for neuroprotection after CA. Therapeutic hypothermia (TH) is the only proven treatment to date to decrease the burden of neurological injury.[3] Better understanding of the underlying mechanism for I/R brain injury after CA is essential for the development of new therapeutic targets and neuroprotective strategies. Here, we review the inflammatory processes involved in I/R after CA. We also review the potential neuroprotective effects of TH in regard to brain inflammation.

Pathophysiology of Brain Injury after Cardiac Arrest

Central nervous system receives almost a third of the cardiac output. Brain injury after CA occurs through several phases. Cerebral blood flow stops with CA ("no-flow" period). Global brain ischemia continues throughout mechanical cardiopulmonary resuscitation that can only provide 25%–40% of baseline cerebral blood flow ("partial-flow" period).[4] Successful return of spontaneous circulation (ROSC) will result in additional processes that may also lead to brain damage ("reperfusion" injury).

Excitotoxicity has been recognized as the main pathological basis of brain injury in the acute phase (minutes to hours after CA). Decreased cerebral blood flow and delivery of oxygen and glucose will enhance anaerobic metabolism within minutes of CA. This will result in lactate production and tissue acidosis.[4] Following ROSC, a transient rise in endogenous and exogenous catecholamines will reduce capillary blood flow that will further enhance lactate acidosis.[5] In addition,

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depletion of adenosine triphosphate (ATP) and inhibition of Na^+/K^+-ATPase will result in neuronal depolarization that in turn leads to increased intracellular shift of calcium and hence extracellular glutamate release.[6,7] Increased glutamate will augment membrane depolarization and further intracellular calcium influx.[8] This will activate a cascade of several calcium-dependent enzymatic pathways such as lipases, proteases, and nucleases that will subsequently lead to disintegration of the cell membrane and tissue necrosis.[9] An increase in the expression of immediate early genes, microRNAs, and heat shock proteins is seen during the acute phase and may contribute to brain injury after CA.[10,11] Accumulating evidence shows that enhanced release of excitatory amino acids (such as glutamate) will also increase permeability of mitochondrial membrane and thereby mitochondrial swelling and dysfunction.[11]

Brain ischemia and excitotoxicity initiated in the acute phase will induce neuronal loss in the subacute phase (hours to days after CA) by the activation of apoptotic pathways.[8,12] Activation of cell membrane death receptors (such as FAS receptor by FAS ligand [FASL]) triggers a death-inducing signaling complex that will in turn activate caspases and programmed cell death.[13] Mitochondrial damage will increase the expression of pro-apoptotic BCL-2 family members (such as BCL-2 associated X [BAX]).[14] Cytochrome c released by apoptotic signaling from damaged mitochondria will form an apoptosome that will also activate caspase.[15] In addition, damage to mitochondria activates pro-apoptotic members of protein kinase C (PKC) family such as PKCδ.[16,17] Damage to mitochondria can also result in apoptosis independent of caspase activation.[18] In addition, reperfusion of ischemic brain will lead to massive generation of free radicals such as reactive oxygen species (ROS).[19,20] Ischemia-induced mitochondrial damage and oversaturation of the cellular scavenging systems will decrease clearance of ROS and result in their accumulation.[21]

Therapeutic considerations

In the acute phase after CA, early resuscitation and restoration of cerebral blood flow will prevent rapid depletion of brain energy reservoir and hence limit anaerobic metabolism and lactic acidosis. This will ultimately decrease excitotoxicity and the subsequent brain damage. During the subacute phase, inhibition of intrinsic and acquired apoptosis by blocking expression of pro-apoptotic genes, increased expression of anti-apoptotic, and alteration of PKC pathway are the potential therapeutic considerations. Brain ischemia activates several signaling pathways such as members of mitogen-activated protein kinases (MAPKs), nuclear factor-kappa B (NF-κB), and toll-like receptors (TLRs) that can be targets for therapeutic interventions.[22-26] Different members of the MAPK pathway play differential roles in brain injury after ischemia. For instance, ERK5 activity seems to be protective while ERK1/2, c-Jun N-terminal kinase (JNK), and p38 may add to brain damage by increasing inflammation.[27-33] Accordingly, inhibition of ERK1/2, JNK, and p38 has been shown to decrease brain inflammation and improve functional recovery.[34-37] Stimulation of ERK1/2 pathway, however, may also paradoxically reduce injury by blocking apoptosis and release of trophic factors after global brain ischemia.[38] Activation of NF-κB family members by ischemia leads to gene transcription for several pro-inflammatory as well as some neuroprotective mediators. Therefore, inhibition of NF-κB activity has also resulted in contradictory results.[39,40] In animal studies, activation of TLRs before induced ischemia decreases brain injury by decreasing release of tissue necrosis factor (TNF)-α; however, it appears that blockage of TLRs is neuroprotective after ischemia.[40,41] In addition, strategies aimed toward enhanced clearance of ROS and limiting damage to blood–brain barrier (BBB) by blockage of proteases will be important in the prevention of secondary brain damage due to vasogenic edema and elevated intracranial pressure.

Brain Inflammation and Immunomodulatory Therapies after Cardiac Arrest

Immune response and inflammatory processes start immediately after onset of ischemia and evolve through several phases.[42] Our understanding of inflammation after global brain ischemia is partly derived from the expanding knowledge on inflammation after focal brain ischemia although differences exist.[43] It is very important to mention that the immune response and cerebral inflammation are not merely consisted of deleterious mechanisms that will result in brain damage (maladaptive inflammation) but also include very important processes required for brain repair and recovery (adaptive inflammation).[44,45] This needs to be considered in all therapeutic measures designed to modulate the immune response to limit maladaptive processes and enhance beneficial immune response. The balance between these responses will determine the ultimate outcomes. Inflammatory processes involved in I/R brain injury after and corresponding therapeutic considerations are summarized in Table 1.

Therapeutic considerations

Given the pivotal role of inflammatory processes in pathogenesis of I/R brain injury, controlled modulation of immune response provides a wide range of therapeutic opportunities for neuroprotection and neuronal repair and thereby improves clinical outcomes. Accordingly, various immunomodulating strategies have been

Table 1: Pathophysiology of ischemia-reperfusion injury and effects of therapeutic hypothermia

Time course	Pathophysiology	Effect of therapeutic hypothermia
Acute (min–h)	Reduced cerebral blood flow and delivery of O_2 and glucose	Decreases metabolic demand, energy preservation
	Promotion of anaerobic metabolism and lactic acidosis	Decreases anaerobic metabolism and lactic acidosis
	ATPase failure, cellular depolarization, increased intracellular calcium influx	Decreases intracellular calcium influx
	Release of excitatory amino acids and glutamate (excitotoxicity)	Increased expression of glutamate receptor subunit 2 of the AMPA receptor and limits excitotoxicity
	Increased expression of immediate early genes and stress signaling	Decreased expression of immediate early genes
	Membrane and mitochondrial damage and dysfunction	
Subacute (h–days)	Activation of NF-κB and MAPK pathways; Expression of adhesion molecules	Inhibits NK-□B and MAPK signaling pathways, limits expression of adhesion molecules
	Production of reactive oxygen species	Decreases reactive oxygen species
	Increased apoptosis (increased BAX, PKCδ, FAS/FASL, and caspase activation)	Inhibits apoptosis (increases BCL-2, PKCε)
	Microglia activation (M1) and Infiltration of neutrophils and monocytes into the brain	Limits microglial activation (M2)
	Release of pro-inflammatory mediators (IL-1, IFN-γ, TNF-α, nitric oxide, ROS, etc.,)	Decreases infiltration of peripheral immune cells
	Blood–brain barrier and endothelial damage by increased proteolytic enzyme activity (elastase, MMP, etc.,)	Decreases pro-inflammatory mediators (IL-1 β TNFα, MCP-1, and MIP3α)
	Increased expression of aquaporin-4 and vasogenic edema	Decreases activity of MMPs and preserves pericytes and blood-brain-barrier
		Decreases expression of aquaporin-4 and vasogenic edema
Chronic (days–weeks)	Release of trophic factors IGF-1, BDNF, GDNF, etc.,	Increases release of neurotrophic factors and expression of genes involved in neurogenesis, angiogenesis, and synapse formation
	Stem cell activation	
	Neurogenesis, angiogenesis, synaptogenesis	

MAPK: Mitogen-activated protein kinases, PKC: Protein kinase C, IFN: Interferon, TNF: Tissue necrosis factor, ROS: Reactive oxygen species, MMP: Matrix metalloproteinases, IGF: Insulin-like growth factor, GDNF: Glial cell-derived neurotrophic factor, BDNF: Brain-derived neurotrophic factor, NK: Natural killer, BAX: Bcl-2-associated X protein, FAS: First apoptosis signal, FASL: FAS ligand, MIP: Macrophage inflammatory proteins, BCL: B-cell lymphoma, MCP: Monocyte chemoattractant protein

investigated in different clinical and animal settings with mixed results. Majority of these interventions have been studied in ischemic or hemorrhagic strokes and studies aiming global brain ischemia after CA are mostly lacking. Therefore, in interpretation of animal results and extrapolation of findings to clinical trials, one should consider the brain injury model and possibility of different underlying mechanisms for focal versus global ischemia. In addition, immunomodulating therapies for brain inflammation after I/R need to be approached cautiously and be tailored carefully to enhance the beneficial immune response while limiting the destructive components. This necessitates careful implementation of basic research findings in regard to timing, aggressiveness, and selectivity of immunomodulatory treatments.[46] Temporal course of potential treatments is of the utmost importance to limit damaging processes and enhance those promoting neuronal repair. Ideally, these treatments are provided early and their effects are limited to the pro-inflammatory (acute to early subacute) phase of immune response. Of note, systemic inflammatory response after CA and brain ischemia can result in a temporary immunocompromised state consisted of peripheral lymphopenia. This can be mediated by overactivation of the hypothalamus–pituitary–adrenal gland axis secondary to catecholamine surge and apoptosis of lymphocytes.[47-49] While this state can potentially limit neuronal damage by immune response, it temporarily increases the risk of infections. Although the role of preexisting systemic or nervous system inflammation is less clear and may affect therapeutic options, it is postulated that systemic inflammation exacerbates brain injury. Potential strategies include blockage of pro-inflammatory and promotion of anti-inflammatory mediators. In addition, modulations of immune cells involved in brain inflammation such as inhibition of brain intrinsic microglial activation, prevention of systemic immune cells transmigration into brain parenchyma, and limiting the activity of infiltrated immune cells have been proposed. Of note, no pharmacological treatment has been approved for clinical use till date.

Acute and subacute cerebral inflammation after cardiac arrest

Immune response is not antigen specific and is dominated by nonspecific pro-inflammatory mechanisms during the acute phase (minutes to hours after CA). This involves activation of brain microglia, massive release of pro-inflammatory mediators, and infiltration of peripheral immune cells, leading to brain inflammation. A vicious cycle of inflammation can evolve in the next several hours to days (subacute phase) triggered by

additional release of inflammatory mediators from activated intrinsic and extrinsic immune cells. Extensive neuronal death, damage to BBB, and worsening cerebral edema will ensue. Both cellular and humoral components of immune response are involved. Our understanding of the complex interaction among innate and adaptive immune system and the brain is still evolving. Enhanced inflammatory response is thought to help with the removal of cell debris but also contributes to additional injury by both direct cell toxicity and release of pro-inflammatory chemokines and cytokines. For instance, while decreased infiltration of the brain by immune cells is associated with smaller infarct size, it may also lead to higher rates of hemorrhagic transformation of ischemic brain.[50,51]

Humoral immune response is mediated by multiple immune mediators after I/R injury. Pro-inflammatory mediators include several cytokines such as interleukin (IL)-1α, IL-1 β, and TNF-α.[52,53] Exogenous administration of IL-1 β after focal ischemic injury has been shown to increase infarct size in animals.[54] Several pro-inflammatory chemokines are also released after ischemia including CX3CL1, MCP-1, and MIP-1α that will aggravate brain injury by increasing permeability of BBB.[55] Other important pro-inflammatory mediators released after brain ischemia are matrix metalloproteinases (MMPs),[56] especially MMP-9,[57] that disrupt BBB and thereby increase brain edema[58] and risk of bleeding into infarcted brain tissue.[59,60] On the other hand, various anti-inflammatory mediators are also released after brain ischemia.[61] Release of IL-10 by T helper 2 (Th2) lymphocytes can inhibit the effects of IL-1 and TNF-α.[62,63] For instance, knockout IL-10 mice and humans with decreased levels of IL-10 develop larger infarcts after focal ischemia.[64-67] Transformation growth factor-β (TGF-β)[68-70] and insulin-like growth factor 1 (IGF-1)[71,72] are among other anti-inflammatory mediators that exert neuroprotective properties.

Modulation of humoral immunity

Several studies have investigated humoral immunity and inflammatory mediators as therapeutic targets. Infarct size was reduced in mice knockout for IL-1α/β and their receptor IL1-receptor 1.[73-76] Administration of IL-1 receptor antagonist, rhIL-1ra, was found to be safe and effective in a phase 2 clinical study of ischemic stroke.[77] Exogenous recombinant IL-6 has been shown to be protective in rats by decreasing inflammation.[78] While experimental blockage of TNF-α limits brain injury, its expression may also be protective against ischemia.[79,80] The paradoxical effects of TNF-α can be explained by the activation of different downstream receptors that exert toxic versus protective properties by activation of caspases[81] versus NF-κB pathway,[82] respectively. Inhibition of pro-inflammatory chemokines has been promising in animal models of brain ischemia not only by reducing inflammation and limiting damage to BBB but also by activation of stem cells.[83] Decreased MMP-9 activity has been shown to be protective against acute injury.[84-88] However, interventions affecting MMPs need to be approached carefully given that their activity is presumed to be protective during the recovery phase.[89] Anti-inflammatory mediators have also been investigated for treatment of I/R injury. Increased levels of IL-10 have been shown to be protective against focal brain ischemia in animals, but clinical studies are lacking.[90-93] Increased expression of TGF-β and IGF-1 suppresses activity of Th1 and Th2 lymphocytes and enhances regulatory T-cells (Treg cells) and thereby can be neuroprotective after ischemia in animals.[68,72,94-97] However, their role in humans and especially after global I/R injury is yet to be determined.

Cellular immune reactions are mediated by both brain intrinsic microglia and infiltrating peripheral leukocytes. Neuronal loss and injury induced by I/R will activate dormant brain intrinsic microglia within minutes of ischemia by stimulation of their surface TLRs.[98,99] Enhanced activity of microglia has been shown to last for weeks after the initial insult.[100] During the acute phase, activated microglia convert into a pro-inflammatory (M1) phenotype that obtains macrophage-like properties (such as antigen presentation) and generates several pro-inflammatory mediators (such as IL-1 β, TNF-α, and ROS) and MMPs that can disrupt BBB.[101] Inhibition of microglial activation in experimental models (for instance, by minocycline)[102,103] has been shown to be neuroprotective, but supportive data in humans are lacking.[104] Ischemia will also activate brain astrocytes that release additional pro-inflammatory mediators such as chemokines, cytokines, nitric oxide, and ROS.[105] Additional immune mediators are released due to systemic inflammatory response induced by systemic ischemia and catecholamine surge after CA. These mediators activate the bone marrow hematopoietic system that is reflected by a decrease in spleen size after brain ischemia and increased release of the immune cells into peripheral bloodstream.[106,107] Accordingly, splenectomy before brain ischemia in animal studies has been shown to decrease infiltration of immune cells into the brain tissue.[108] Increased expression of several members of selectin family on the surface of endothelium (E-selectin), leukocytes (L-selectin), and platelets (P-selectin) along with increased expression of intracellular and vascular adhesion molecules (ICAM-1 and VCAM-1) facilitates entry of peripheral immune cells into the brain after ischemia through damaged endothelium and BBB.[109-111] Accordingly, levels of P- and E-selectin and ICAM-1 are correlated with severity of stroke.[112-114] Peripheral neutrophils migrate first, followed by macrophages and later natural killer (NK)

cells and lymphocytes.[115-117] Neutrophils infiltrate the brain as soon as 30 min after ischemia and release additional pro-inflammatory cytokines and enzymes such elastase, granzyme A, myeloperoxidase, and MMPs that will worsen brain inflammation and further disrupt BBB.[36-38] In addition, nitric oxide production will increase by activation of inducible isoform of nitric oxide synthase.[118-120] Macrophages and peripheral monocytes contribute to both pro- and anti-inflammatory processes after ischemia. Pro-inflammatory monocytes (such as Ly-6C^{high}/CCR2+ subpopulation) egress into the brain and some develop macrophage-like features inside the nervous tissue.[121] Infiltrating lymphocytes and their subtypes play a complex role in brain inflammation after ischemia.[122,123] NK cells and CD4$^+$ and CD8$^+$ T-lymphocytes not only cause neuronal damage by direct cytotoxicity but also exaggerate excitotoxicity by releasing factors such as IL-1 β, IL-17, interferon-γ (IFN-γ), TNF-α, and ROS.[116,124,125] Release of IFN-γ and granulocyte-macrophage-colony-stimulating factor by NK cells will further activate macrophages, microglia, and astrocytes and leads to a vicious cycle of inflammation in the central nervous system. In addition, increased expression of aquaporin-4 that regulates water transport along with increased activity of MMP and permeability of disrupted BBB and endothelium will lead to vasogenic edema and increased risk of hemorrhage and thereby increased intracranial pressure that can cause additional brain damage.[105,126-128]

Modulation of cellular immunity

Various lines of immune cells are involved in brain injury after I/R. Therefore, several animal and human studies have investigated cellular immunity as a therapeutic target. Decreased entry of peripheral immune cells into ischemic brain tissue may result in decreased inflammation and better outcomes. Inhibition of adhesion molecules such as P- and E-selectin and ICAM-1 has been shown to be protective against focal ischemia in animals.[129-133] Blocking L-selectin also appears to be protective against I/R injury.[134,135] However, results of clinical trial in preventing transmigration of peripheral immune cells into the nervous system have been disappointing. Administration of selective monoclonal antibodies against ICAM-1 (enlimomab), CD11b/CD18, and recombinant neutrophil inhibitory factor resulted in no protection and even worsened outcomes.[77,136] Lack of desirable clinical outcomes has been attributed to the selection of antibody. Role of interventions toward VCAM-1 is unclear, and contradictory results have been reported.[137,138] Although administration of oral minocycline to modulate early inflammatory response was promising in earlier trials, a phase 4 trial was terminated due to futility.[139,140] Similarly, despite encouraging results of preliminary studies on the administration of α4-integrin antibody natalizumab after focal ischemia, no significant clinical benefit was found in a recent clinical trial.[141] Fingolimod, an S1P receptor agonist, has been shown to decrease infiltration of lymphocytes into brain and activation of brain microglia.[142] Combination of fingolimod and alteplase in a pilot trial of ischemic stroke has shown improved clinical outcomes.[143]

Chronic cerebral inflammation after cardiac arrest

Inflammatory processes during this phase (days to weeks after CA) stimulate pathways involved in neuronal repair and play an important role in brain recovery. Regulatory mechanism will lead to gradual resolution of the immediate inflammatory response. Microglia assume an anti-inflammatory (M2) phenotype, assist with a clearance of the cell death products,[144,145] and secrete anti-inflammatory immune mediators (such as IL-10 and TGF-β) that can subside pro-inflammatory processes and exert neuroprotection.[146,147] They also promote neuronal repair, prevent premature death of neural stem cells, and enhance neurogenesis and neurite growth by secretion of growth factors such as IGF-1 and glial cell line-derived neurotrophic factor.[148-151] Activated astrocytes play an anti-inflammatory role as well.[152-155] Anti-inflammatory monocytes (such as Ly-6C^{low}/CCR2-subpopulation and Treg cells) also release anti-inflammatory cytokines such as IL-10.[156,157] Ultimately, neurogenesis, angiogenesis, and synaptogenesis will result in functional recovery.[158]

Therapeutic Hypothermia and Brain Inflammation after Cardiac Arrest

TH is the only approved treatment to date for neurological injury after CA. Neuroprotective properties of hypothermia have been known for the past three decades;[159] however, clinical application of TH to protect brain after CA was widely adopted after two large prospective clinical trials.[160,161] Several factors are to be considered in application of TH as a neuroprotective measure.[162] Choosing the optimal temperature is of paramount importance to provide neuroprotection and avoid undesirable adverse effects. It appears that milder reductions in core body and brain temperature can be as effective as lower temperatures.[163] In clinical settings, targeting core temperature of 32°C–34°C was initially recommended for comatose patients with out-of-hospital CAs due to shockable rhythms. However, more recent evidence suggests that targeted temperature management and avoidance of hyperthermia may exert the same clinical benefits.[164] Early application and sufficient maintenance of TH are also important to achieve maximum neuroprotection and improve outcomes.[3] Here, we review the beneficial and neuroprotective effects of TH in regard to cerebral inflammation after CA [Table 1].

Therapeutic hypothermia during acute phase after ischemia-reperfusion injury

In the first several minutes of I/R after CA, early implementation of TH will decrease the metabolic demand and activity of neurons and thereby extends preservation of energy reservoir and prevents shift toward anaerobic metabolism and lactic acidosis.[165] In addition, TH increases expression of glutamate receptor subunit 2 of the AMPA receptor. Upregulation of this subunit reduces influx of calcium after I/R. The subsequent decrease in intracellular calcium level and glutamate release will dampen excitotoxicity.[166,167] Hypothermia also reduces expression of immediate early genes, stress signals, and microRNAs; however, the significance of these changes in neuroprotection is not clear.[10,168-170] Neuroprotection by TH can also be provided by decreased generation of ROS due to blunting cerebral blood flow after reperfusion.[171,172] In addition, by reducing activity of neuronal and inducible isoforms of nitric oxide synthase, TH decreases production of nitric oxide.[173,174]

Therapeutic hypothermia during subacute phase after ischemia-reperfusion injury

The beneficial effects of TH extend beyond the acute phase. As described above, I/R leads to neuronal apoptosis via multiple pathways. TH, on the other hand, can prevent apoptosis via both caspase-dependent and caspase-independent pathways.[175] Hypothermia has been shown to inhibit translocation of apoptosis-inducing factor from mitochondria.[176-178] It also shifts the balance toward stimulation of anti-apoptotic mechanisms (such as BCL-2 and PKCε) and reducing activity of pro-apoptotic processes (such as BAX, PKCδ, and FAS/FASL).[179-183] By increasing BCL-2, TH activates the serine/threonine protein kinase AKT that is involved in cell survival and proliferation.[181,184] Most importantly, TH limits the maladaptive inflammatory response during subacute phase after CA that leads to better outcomes.[185,186] Hypothermia exerts its anti-inflammatory properties on multiple immune cells and mediators. It decreases activation of microglia and recruitment of immune cells into ischemic brain tissues.[187] It also inhibits NF-κB and MAPK signaling pathways and expression of adhesion molecules involved in ischemia-induced inflammation.[185,188-193] Release of various pro-inflammatory cytokines (such as IL-1 β and TNFα) and chemokines (such as MCP-1 and MIP3α) is also reduced by TH.[194-198] However, TH will also reduce anti-inflammatory mediators such IL-10 and TGF-β.[195,199] As discussed above, disruption of BBB by inflammation after I/R injury leads to brain edema and hemorrhagic conversion within infarcted tissues that will eventually cause secondary damage by elevation of intracranial pressure. Hypothermia has been shown to decrease BBB disruption in various brain pathologies. The underlying mechanism for BBB protection by TH is presumed to be decreased proteolytic activity of enzymes such as MMPs and release of MMP inhibitors, as well as preservation of endothelial cells and pericytes.[200-206] Hypothermia can decrease brain edema by decreased expression of aquaporin-4 after global brain ischemia.[128,207,208]

Therapeutic hypothermia during chronic phase after ischemia-reperfusion injury

Hypothermia also affects the chronic phase (days to weeks) after I/R brain injury. It has been shown to increase the level of several neurotrophic factors such as brain-derived and glial-derived neurotrophic factors that are involved in neuronal recovery.[209-211] Despite some conflicting reports, it seems that mild hypothermia (as opposed to deep hypothermia with temperatures below 30°C) enhances activity of stem cells and their differentiation into neurons and glial cells after brain ischemia likely by inhibition of apoptosis.[212-217] However, the optimal parameters for hypothermia to promote neurogenesis and whether this effect applies to aged individuals are yet to be determined. Hypothermia limits injury to oligodenrocytes and enhances their proliferation after brain injury.[213,218] The net effect for increased activity and number of astrocytes by TH after brain injury are not clear. While generation of new astrocytes may be required for brain regeneration, it may also lead to formation of glial scars and interfere with neurogenesis and synaptogenesis.[219] Hypothermia also promotes angiogenesis after brain injury although its clinical benefit has not been proven and can even impair recovery.[175,220,221] Formation of new neuronal connections (synaptogenesis) is an important part of recovery after extensive brain damage. Hypothermia appears to enhance this process by upregulation of genes required for synapse formation.[220,222-224]

Current Perspectives and Future Directions

Despite astounding evidence for the role of inflammation in pathogenesis of I/R injury and encouraging animal data, TH remains the only proven treatment to date for neuroprotection after CA. Several clinical trials based on animal findings or preliminary clinical data have failed to show benefits and some resulted in worsened outcomes. Complex pathophysiology of I/R injury, in general, and unknown interactions among different components of immune response, in particular, are likely to be responsible for poor translation of bench findings into meaningful bedside trials. In addition, results of animal models from one brain pathology (for instance, brain hemorrhage or focal ischemia) shall be cautiously generalized to another disease (such as global brain ischemia). Even in animal models for global ischemia, it appears that some modifications are required to

better reflect the complexity and realities of global brain ischemia in humans. Aging brain, gender-specific factors, and common comorbidities need to be incorporated into animal studies. In regard to immunomodulatory treatments including TH, careful timing of therapeutic interventions is of critical importance. At times, modulation of an immune mediator can result in different outcomes based on timing and activated downstream pathways. As described above, inflammatory processes after brain injury have significant overlap and affecting a single component may not be sufficient to overcome the redundancy. Combination of different therapeutic modalities (such as TH with antibodies against immune cells or mediators) to affect multiple mechanisms simultaneously may be advantageous. While many of the clinical studies targeted blockage of pro-inflammatory mediators and peripheral immune cells, more focus on brain intrinsic microglia and enhancement of anti-inflammatory mediators may result in better outcomes. In addition, application of newer technologies such as molecular imaging and advanced multi-modal MRI in design and interpretation of clinical studies may be helpful.

Conclusions

Inflammation after CA plays a major role in pathophysiology of brain I/R injury. Modulation of brain inflammation provides a wide range of therapeutic options. TH is the only proven treatment to date that affects multiple aspects of brain inflammation after CA. Further animal and clinical studies are required to identify other treatment options.

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Conflicts of interest
There are no conflicts of interest.

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