Hypothermia promotes synaptic plasticity and protective effects in neurological diseases

Hypothermia has been recommended for neurological treatment since the ancient world.[1] The Greek physician Hippocrates noticed that infants exposed in the open survived longer in the winter months than in the summer.[1] Several centuries later, the physiologists Claude Bernard and William Edwards noticed that asphyxiated newborn kittens gasped for a longer time period when actively cooled.[2] During the 1950s and 1960s, uncontrolled studies were performed on infants with severe hypoxia, who were unable to breath 5 min after birth.[3] The infants were immersed in cold water until they were able to begin respiration and outcomes were reported better than controls.[4] However, case reports indicated that cooling caused subcutaneous fat necrosis with calcification[5] and there were higher oxygen requirements and greater mortality rates among premature newborns that were kept hypothermic after birth.[6] This approach was eventually overtaken by the development of active resuscitation techniques, leading to a pause in investigations for therapeutic hypothermia on asphyxiated neonates.[1] However, there has been a resurgence in research on hypothermia's potential for effective treatment on mild perinatal asphyxia.[1]

Perinatal asphyxia is a major cause of death and neurological impairment in newborn infants, with an estimated incidence of 1/1,000 live births in resource-rich countries.[7] Hypothermia has shown evidence as a possible neuroprotective treatment. Gunn *et al*. indicated that hypothermia causes neuroprotection on near-term fetal sheep with cerebral ischemia by preventing cytotoxic edema and, thus, reducing neural loss.[8] Another study by Lei *et al*. demonstrated that canines that underwent hypothermia after CA-induced ischemia and resuscitation inhibited both the peroxidation of membrane lipids and the production of free radicals in the brain tissue, proving that the treatment prevented ROS damage.[9] Edwards *et al*. uncovered that newborn piglets who experienced transient cerebral ischemia and postinsult hypothermia reduced the amount of apoptotic cells in the cingulate sulcus, signifying that hypothermia inhibits the apoptotic pathway.[10] In addition, a study by Thoresen *et al*. noted that newborn piglets who underwent transient brain ischemia and postischemic hypothermia reduced the typical increase in excitatory amino acids (EAA) and NO in the cerebral cortex.[11] This indicated that hypothermia protected mitochondrial oxidative phosphorylation from the EAAs and also attenuated inflammation due to the lowered NO levels.[11] Haaland *et al*. provided evidence that mild hypothermia can reduce the severity of brain damage that results from moderate hypoxic-ischemic insults in newborn piglets.[12] Although hypothermia has proven to have neuroprotective benefits on perinatal asphyxia, it also presents with its limits as well.

Hypothermia has also been observed to have limitations when treating perinatal asphyxia. For cooling to be effective, it must be given under certain parameters: begun within 6 h of age, infant cooled to 33.5°C for 72 h, and then rewarmed for at least 4 h.[13] Cooling deeper to 32°C and/or cooling longer to 5 days has not shown to be more beneficial.[13] Furthermore, treatment was nonresponsive to the more severe forms of hypoxia-ischemic insults.[13] It is not known if therapeutic hypothermia can be harmful to nonencephalopathic infants or those with severe infections.[13] Cooling has been noted to worsen outcomes of neonates that are also experiencing ongoing hemorrhage.[13] It has also been shown to possibly worsen asphyxia-associated coagulopathy and cause pulmonary hypertension.[14] Hypothermia is known to prolong the QT interval, which can potentially induce an arrhythmia.[14] Sinus bradycardia is the most common symptom observed in infants treated with moderate cooling.[14] The interval between the end of the hypoxia-ischemic exposure and the beginning of the hypothermic therapy influences the treatment's neuroprotective ability, where infants cooled after 6 h from birth begin to have diminished benefit.[15] Although moderate cooling proves to be effective against transient asphyxia in term infants, preterm infants oddly experience an increase in mortality even when the cooling is mild.[15] Davidson *et al*. noted that hypothermia following temporary asphyxia in preterm fetal sheep caused a prolonged increase in the cortisol response while not affecting the increase in adrenocorticotropic hormone levels. As high cortisol levels have been correlated with neonatal hypotension, it is hypothesized that this could contribute to the marked increase in mortality.[15] Reflecting on this response to mild neonatal asphyxia, the impact of hypothermia has also been investigated in its potential to restore synapses and promote neuroprotection in neurological diseases.

During mammalian hibernation, it has been observed that neural synapses dismantle when the body temperature

is cooled, and synapses regenerate when normal body temperature is regained.[16] This hypothermic period induces the production of cold-shock proteins, particularly ribonucleic acid (RNA)-binding motif protein 3 (RBM3).[17] To generate RBM3, cooling causes neuronal release of brain-derived neurotrophic factor (BDNF), which activates tropomyosin receptor kinase B (TrkB).[18] Consequently, TrkB activates the phospholipase Cγ1(PLCγ1) protein, which activates the cAMP Response Element-Binding (CREB) protein protein that inhibits the phosphorylated extracellular signal-regulated kinase (p-ERK) protein, causing increased expression of RBM3.[18] RBM3 has been observed to function in neuroprotection during hypothermic conditions by preventing neural cell death and improving synaptic plasticity.[19] This protein does so by increasing local protein synthesis at dendrites[20] and global protein synthesis through binding ribosomal subunits and/or by micro RNA biogenesis.[21] Specifically, RBM3 is shown to bind the messenger RNA of the cold-shock protein reticulon 3 (RTN3) and upregulate its expression.[22] RTN3 functions in a neuroprotective role as it is involved in promoting synapse formation and synaptic plasticity.[23] Synaptic plasticity is defined as the ability to modify the strength or efficacy of synaptic communication between preexisting synapses in response to their use or disuse, which is often compromised in neurological diseases.[23] Hypothermia has thus been used as a treatment to help alleviate the symptoms of deleterious neurological conditions such as neurodegenerative disease,[24] traumatic brain injury (TBI),[24] and cardiac arrest (CA)-induced ischemic stroke.[25] This commentary will examine the effects of hypothermia on synaptic plasticity on these various neurological conditions.

Neurodegenerative diseases, such as Alzheimer's disease and prion disease, lead to a progressive loss of synapses and neurons, causing a decline in cognitive ability.[24] Peretti *et al.* performed an experiment to determine whether increasing RBM3 expression would restore the failed synaptic plasticity in mice with Alzheimer's disease or prion disease.[19] The utilization of hypothermia to increase RBM3 expression in mice with prion disease was shown to prevent loss of synapses, improve synaptic communication, and thwart behavior deficits.[19] In addition, prion-infected mice that were exposed to hypothermic conditions were observed to have a prolonged lifespan compared to the ones that were not.[19] RBM3 knockdown through lentiviral-mediated RNAi eliminated the neuroprotective effects of hypothermia on prion disease in mice.[19] To confirm RBM3 role in neuroprotection, RBM3 was either overexpressed through lentivirus LV-RBM3 or reduced through the lentivirus LV-shRNA-RMB3, without the influence of hypothermic conditions.[19] LV-RBM3 treatment promoted neuroprotection in prion-infected mice and in mice with Alzheimer's disease, causing an increase in their lifespan.[19] LV-shRNA-RBM3 treatment caused an earlier onset of synaptic degeneration, loss of neurons, and behavioral deficits in mice of both neurodegenerative diseases, causing a decrease in their lifespan.[19] Along with neurodegenerative diseases, the effects of neurological cooling were also investigated in TBIs.

TBI is the leading cause of death and disability for individuals under the age of 45.[26] TBIs cause brain dysfunction due to a vast degeneration of dendrites and spines and a significant reduction in synapses.[27] Symptoms of TBI include psychiatric/behavioral, neurological, and physical disturbances.[28] Liu *et al*. performed a study to determine whether hypothermic pretreatment can improve the cognitive impairment caused by TBI in mice.[29] Mice that underwent a hypothermic pretreatment were observed to restore the learning and memory impairment caused by a TBI compared to mice with normothermic pretreatment.[29] In addition, mice that underwent hypothermic pretreatment to TBI recovered the reduction in dendritic spines and synaptic plasticity unlike in normothermic controls.[29] Precooled mice, with both sham and TBI treatment, showed an increase in the postsynaptic proteins PSD93, PSD95, and NR2B compared to normothermic pretreated mice.[29] These synaptic proteins are known to promote synaptic plasticity, learning, and memory.[29] In addition to TBI, hypothermia was also investigated in alleviating the symptoms of CA-induced ischemia.

CA is a tragic event that has a high morbidity rate.[30] This event causes global ischemia and neurological injury in those who survive, leading to a lifetime of dependency.[30] Hypothermia is the only known treatment that can improve neurological outcomes and survival in neonates and adults that have experienced CA.[25] However, it is unclear why hypothermia does not increase survival for children with this same condition.[25] Dietz *et al*. conducted a study to uncover how hypothermia affects juvenile mice that have experienced CA-induced ischemia and cardiopulmonary resuscitation (CPR) (CA/CPR).[25] As neurons have the innate ability to undergo synaptic plasticity (long-term potentiation), this was measured to evaluate neural function.[25] Hippocampal slices of CA/CPR-operated mice were observed to have decreased long-term potentiation compared to sham-operated mice.[25] This indicates that global ischemia impairs synaptic plasticity in juvenile mice.[25] Hippocampal slices also indicated that hypothermia prevented the reduction in long-term potentiation following CA/CPR-induced ischemia.[25] Interestingly, mice showed sexual dimorphism in their ability to protect against ischemia-induced impairment of synaptic plasticity.[25] Hypothermia at 32°C protected long-term potentiation

more effectively in female mice compared to male mice.[25] Male mice required a deeper level of hypothermia at 30°C for equal protection.[25] Likewise, this is the first study to demonstrate that hypothermia can preserve synaptic plasticity following global ischemia.[25]

In conclusion, hypothermia has been consistently shown to improve synaptic plasticity and promote neuroprotection in neurological diseases. Lui *et al*. articulated that there is another dimension when utilizing hypothermia as it could be an effective treatment not only post-TBI but also pre-TBI.[29] This provides a novel consideration to where subjects at risk of neurological harm could reduce their damage if pretreated with hypothermia. The effects of hypothermia also prove to be complex as Dietz *et al*. indicated that hypothermia is able to improve synaptic plasticity following ischemic stroke in juvenile mice when it is not observed to do so in children, while also observing a sexual dimorphic response to treatment.[25] It is clear that more studies will be needed to have a better mechanistic understanding of why hypothermia affects juvenile mice differently than in children and to why male and female mice have different responses. Moreover, as Peretti *et al*. demonstrated that the significance of hypothermia treatment is based on the production of the RBM3 protein,[19] this provides a new direction to where inducing RBM3 expression can suffice to improve synaptic plasticity without needing to cool the subject. This will promote neuroprotection without the negative side effects that come along with cooling, which could lead to expanding the limited circumstances of when neonates could receive treatment for neonatal asphyxia. The potential of hypothermia to treat neurological diseases in humans is promising and should be further examined.

Conflicts of interest

Dr. Yuchuan Ding is an Associate Editor of *Brain Circulation*. The article was subject to the journal's standard procedures, with peer review handled independently of this Editor and their research groups.

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