Therapeutic Hypothermia and Targeted Temperature Management With or Without the “Cold Stress” Response

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IN THIS ISSUE of *Therapeutic Hypothermia and Temperature Management*, Choudhary and Jia (2017) present a review of studies that have explored approaches to reduce and regulate temperature in a manner that circumvents the need for “forced” temperature manipulation. The approaches reviewed include activation or inhibition of specific hypothalamic nuclei via pharmacologic strategies and/or using electrical stimulation. The pharmacologic approaches described range from direct neurotransmitter manipulation such as of α_1 or α_2 receptors or manipulation of nitric oxide synthetic pathways by microinjection of either noradrenaline or *N*-monomethyl-L-arginine (L-NMMA), respectively, into the hypothalamus (Mallick *et al.*, 2002; Osaka, 2010) or local infusion of vasopressin 1A-receptor agonists to modulate “warm sensitive” (WS) or “cold sensitive” (CS) neurons (Tang *et al.*, 2012). More clinically relevant approaches include systemic administration of drugs such as neurotensin (Katz *et al.*, 2015), cannabinoids (Ma *et al.*, 2014), thyroxine derivatives (Doyle *et al.*, 2007), hydrogen sulfide (Lefer, 2007), adenosine, or many others have been suggested (also reviewed in Zhang *et al.*, 2013; Liu *et al.*, 2016), as has electrical stimulation of selected hypothalamic nuclei (Choudhary and Jia, 2017). However, not all approaches have been successful or easy to replicate across various models of acute brain injury and resuscitation—where they might be the most useful, and importantly work in large animal models—where cooling is more challenging than in rodents is more limited and more variable in success (Drabek *et al.*, 2011; Katz *et al.*, 2012).

Notably, the majority of evidence supporting the concept that manipulation of hypothalamic circuits is a promising strategy to induce neuroprotection is derived from experiments in which animals were uninjured. More work is needed to test if hypothalamic pathways can be similarly manipulated after damage in different types of brain injury. Hypothalamic insufficiency is well known to occur after a traumatic brain injury (TBI) (Schneider *et al.*, 2017), and the extent of hypothalamic damage after other insults relevant to therapeutic hypothermia (TH) and targeted temperature management (TTM) such as cardiac arrest need to be further clarified. Elucidation of the mechanisms that mediate hypothalamic/pituitary dysfunction postinjury is an ongoing area of investigation. Clinical translation of hypothalamic

modulating strategies, for cooling brain-injured patients, will require additional research to define whether or not synaptic functions of target brain nuclei (e.g., containing WS or CS neurons) remain relatively spared/normal and have predictable pharmacological responsiveness—compared with the spectrum of abnormal states manifested in vulnerable brain regions damaged by injury and which might benefit most from TH. Also, this could differ greatly across the various CNS insults.

Another practical question, to be addressed, is the extent to which pharmacological modulation of hypothalamic circuits is amenable to controlling the rate of rewarming, which would be important to address if these types of therapies were used for a sustained period, for example, to prevent shivering—rather than to induce hypothermia. The 2015 American Heart Association guidelines recommend that patients treated with TH be rewarmed at 0.3–0.5°C/h. Rewarming at faster rates is also known to worsen outcome in TBI patients (Hutchison *et al.*, 2008). It would be interesting to test if drug-induced hypothermia avoids challenges associated with rewarming compared with standard cooling devices; might hypothalamic modulation result in less hemodynamic instability or changes in sympathetic tone during rewarming (Tokunaga *et al.*, 1996)? However, it is unclear in the setting of drug-induced cooling—with resetting of hypothalamic regulation, if residual drug was present, a situation could develop where a return to normothermia might be perceived as induction of “forced” hyperthermia.

Preventing some of the adverse consequences of “forced cooling” or allowing more prompt temperature reductions by blunting endogenous temperature regulation could be highly desirable and beneficial in the application of TH or TTM, as pointed out by the authors. Mitigating complications that result from cold stress, most notably, shivering, could importantly reduce metabolic demands during acute neurologic crises and prevent the cascade of secondary consequences that ensue from preventing or treating this side effect, notably the use of sedatives, narcotics, intubation, mechanical ventilation, and/or neuromuscular blockade, if other more benign strategies to prevent shivering such as surface warming are insufficient or impractical. Clearly, this review confirms that interventions that might facilitate the induction and maintenance of TH and/or TTM deserve additional exploration.

Furthermore, a pharmacological method to rapidly initiate endogenous cooling and/or augment intravenous or surface cooling could have tremendous utility for first responders during the transport of patients, or to augment cooling in the emergency department and/or intensive care unit.

However, it has become newly apparent that there are also novel and unique aspects of the endogenous reaction to TH, namely, newly discovered components of the “cold stress” response that may confer powerful neuroprotective effects. In a provocative report in the journal *Nature* by Peretti *et al.* (2015), a brief (1–2 hours) period of deep hypothermia induced by injection of 5-AMP with cold exposure produced remarkable neuroprotection against long-term neurodegeneration in mice with either an Alzheimer’s disease knock-in phenotype or prion disease (Peretti *et al.*, 2015). In that study, induction of the cold-shock protein RNA binding motif-3 (RBM-3) appeared to represent the key facilitator of this long-term benefit—which included histological and behavioral benefit and prolonged survival.

That report, although extremely exciting, raised many questions about the clinical translatability of these findings, namely neuroprotection by hypothermia-induced RBM-3, particularly, with regards to the use of TH and TTM in acute brain injury and neurocritical care. Our group has provided some insight into that important question. We reported that temperature reductions as small as 1°C induced robust expression of RBM-3 in isolated neurons (Jackson *et al.*, 2015), suggesting this mechanism might play a role in mild TH and/or even TTM. The response was particularly robust in young neurons, mimicking newborn neurons, but largely absent in “adult” neurons. In addition, data suggest that RBM-3 mediates its benefit, at least in part, through potent induction of various facets of global protein synthesis upon rewarming.

Also, because RBM-3 protein levels are robustly increased in large and small hibernating animals (Fedorov *et al.*, 2011; Schwartz *et al.*, 2013), drug-inducing cooling strategies, which activate hibernation regulatory pathways (e.g., adenosine receptor agonists) (Choudhary and Jia, 2017), may similarly increase or perhaps further augment this important neuroprotective mechanism vs. traditional cooling techniques. Also, relevant to the anatomical focus of the review, RBM-3 expression in hibernating ground squirrels is abundant, specifically, in the hypothalamus as well as in cortex during prehibernation, torpor, and during interbout arousal episodes (Schwartz *et al.*, 2013). This finding is logical given that the hypothalamus is a major regulator of mammalian hibernation and because RBM-3 helps cells to function normally under conditions of cold stress (i.e., RBM-3 preserves global protein synthesis—which is a prerequisite for protein cell signaling and thus presumably for the hypothalamus to exert its biological actions).

Taken together, these studies clearly raise important questions, such as (1) how much of the acute or long-term benefit of TH or TTM is modulated by RBM-3 or other cold stress proteins—versus other more traditional and well-known benefits of TH or (2) might we be able to prevent unwanted side effects of “cold stress” such as shivering while maintaining its neuroprotective effects during TH or TTM? It also may be more than coincidence that the RBM-3 is robust in “young” neurons *in vitro*, but minimal in “adult” neurons (Jackson *et al.*, 2015). Clinically, TH is well known to exhibit its greatest degree of neuroprotection in the newborn brain versus

older children or adults (Jacobs *et al.*, 2013; Moler *et al.*, 2016; Tasker *et al.*, 2017). Our work on the mechanism of action of RBM-3 and efforts to develop pharmacological inducers or mimics of it also suggest that drugs such as fibroblast growth factor-21 can induce RBM-3 *in vitro*, so there may even be a hope for a pharmacological avenue to induce this pathway without requiring “cold stress.”

Certainly, TH has long been known to those using it clinically and in preclinical models to represent a complex intervention, with multiple effects inside and outside of the CNS. It not only produces clear potent neuroprotection but also challenging side effects—well beyond shivering, such as impairment of drug metabolism, cold diuresis, alterations in systemic and cerebral hemodynamics, electrolyte abnormalities, alterations in coagulation, and increased infection risk (Tortorici *et al.*, 2007; Hutchison *et al.*, 2008; Fink *et al.*, 2010; Empey *et al.*, 2013; Anderson *et al.*, 2016). This review by Choudhary and Jia (2017), taken along with other exciting molecular developments in the field, thus is timely and serves to increase our awareness that new approaches to inducing and/or augmenting TH and TTM may be on the horizon to take better advantage of both its potent neuroprotective effects while minimizing its complications. It may take just the right dose of cold stress.

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Drs. Kochanek and Jackson are coprovisional patent holders for the United States. Invention disclosure: Title: Method to Improve Neurologic Outcomes in Temperature-Managed Patients.

References

- Anderson KB, Poloyac SM, Kochanek PM, Empey PE. Effect of hypothermia and targeted temperature management on drug disposition and response following cardiac arrest: a comprehensive review of preclinical and clinical investigations. *Ther Hypothermia Temp Manag* 2016;6:169–179.
- Choudhary RC, Jia X. Hypothalamic or extrahypothalamic modulation and targeted temperature management after brain injury. *Ther Hypothermia Temp Manag* 2017;7:125–133.
- Doyle KP, Suchland KL, Ciesielski TM, Lessov NS, Grandy DK, Scanlan TS, Stenzel-Poore MP. Novel thyroxine derivatives, thyronamine and 3-iodothyronamine, induce transient hypothermia and marked neuroprotection against stroke injury. *Stroke* 2007;38:2569–2576.
- Drabek T, Kochanek PM, Stezoski J, Wu X, Bayir H, Morhard RC, Stezoski SW, Tisherman SA. Intravenous hydrogen sulfide does not induce hypothermia or improve survival from hemorrhagic shock in pigs. *Shock* 2011;35:67–73.
- Empey PE, Velez de Mendizabal N, Bell MJ, Bies RR, Anderson KB, Kochanek PM, Adelson PD, Poloyac SM, Pediatric TBI Consortium: Hypothermia Investigators. Therapeutic hypothermia decreases phenytoin elimination in children with traumatic brain injury. *Crit Care Med* 2013;41:2379–2387.

- Fedorov VB, Goropashnaya AV, Tøien O, Stewart NC, Chang C, Wang H, Yan J, Showe LC, Showe MK, Barnes BM. Modulation of gene expression in heart and liver of hibernating black bears (*Ursus americanus*). *BMC Genomics* 2011;12:171.
- Fink EL, Clark RS, Kochanek PM, Bell MJ, Watson RS. A tertiary care center's experience with therapeutic after pediatric cardiac arrest. *Pediatr Crit Care Med* 2010;11:66–74.
- Hutchison JS, Ward RE, Lacroix J, Hebert PC, Barnes MA, Bohn DJ, Dirks PB, Doucette S, Fergusson D, Gottesman R, Joffe AR, Kirpalani HM, Meyer PG, Morris KP, Moher D, Singh RN, Skippen PW; Hypothermia Pediatric Head Injury Trial Investigators and the Canadian Critical Care Trials Group. Hypothermia therapy after traumatic brain injury in children. *N Engl J Med* 2008;358:2447–2456.
- Jackson TC, Manole MD, Kotermanski SE, Jackson EK, Clark RS, Kochanek PM. Cold stress protein RBM3 responds to temperature change in an ultra-sensitive manner in young neurons. *Neuroscience* 2015;305:268–278.
- Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2013;1:CD003311.
- Katz LM, Frank JE, Glickman LT, McGwin G Jr, Lambert BH, Gordon CJ. Effect of a pharmacologically induced decrease in core temperature in rats resuscitated from cardiac arrest. *Resuscitation* 2015;92:26–31.
- Katz LM, McGwin G Jr, Gordon CJ. Drug-induced therapeutic hypothermia after asphyxial cardiac arrest in swine. *Ther Hypothermia Temp Manag* 2012;2:176–182.
- Lefer DJ. A new gaseous signaling molecule emerges: cardioprotective role of hydrogen sulfide. *Proc Natl Acad Sci U S A* 2007;104:17907–17908.
- Liu K, Khan H, Geng X, Zhang J, Ding Y. Pharmacological hypothermia: a potential for future stroke therapy? *Neurol Res* 2016;38:478–490.
- Ma L, Lu X, Xu J, Sun S, Tang W. Improved cardiac and neurologic outcomes with postresuscitation infusion of cannabinoid receptor agonist WIN55, 212–2 depend on hypothermia in a rat model of cardiac arrest. *Crit Care Med* 2014;42:e42–e48.
- Mallick BN, Jha SK, Islam F. Presence of alpha-1 adrenoreceptors on thermosensitive neurons in the medial preoptico-anterio hypothalamic area in rats. *Neuropharmacology* 2002;42:697–705.
- Moler FW, Hutchison JS, Nadkarni VM, Silverstein FS, Meert KL, Holubkov R, Page K, Slomine BS, Christensen JR, Dean JM; Therapeutic Hypothermia After Pediatric Cardiac Arrest Out-of-Hospital Trial Investigators. *Pediatr Crit Care Med* 2016;17:712–720.
- Osaka T. Nitric oxide mediates noradrenaline-induced hypothermic responses and opposes prostaglandin E2-induced fever in the rostromedial preoptic area. *Neuroscience* 2010;165:976–983.
- Peretti D, Bastide A, Radford H, Verity N, Molloy C, Martin MG, Moreno JA, Steinert JR, Smith T, Dinsdale D, Willis AE, Mallucci GR. RBM3 mediates structural plasticity and protective effects of cooling in neurodegeneration. *Nature* 2015;518:236–239.
- Schneider HJ, Kreitschmann-Andermahr I, Ghigo E, Stalla GK, Agha A. Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a systematic review. *JAMA* 2017;298:1429–1438.
- Schwartz C, Hampton M, Andrews MT. Seasonal and regional differences in gene expression in the brain of a hibernating mammal. *PLoS One* 2013;8:e58427.
- Tang Y, Yang YL, Wang N, Shen ZL, Zhang J, Hu HY. Effects of arginine vasopressin on firing activity and thermosensitivity of rat PO/AH area neurons. *Neuroscience* 2012;219:10–22.
- Tasker RC, Vonberg FW, Ulano ED, Akhondi-Asl A. Updating evidence for using hypothermia in pediatric severe traumatic brain injury: conventional and bayesian meta-analytic perspectives. *Pediatr Crit Care Med* 2017;18:355–362.
- Tokunaga S, Imaizumi T, Fukae K, Nakashima A, Hisahara M, Tominaga R, Takeshita A, Yasui H, Tokunaga K. Effects of hypothermia during cardiopulmonary bypass and circulatory arrest on sympathetic nerve activity in rabbits. *Cardiovasc Res* 1996;31:769–776.
- Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: a focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. *Crit Care Med* 2007;35:2196–2204.
- Zhang M, Wang H, Zhao J, Chen C, Leak RK, Xu Y, Vosler P, Chen J, Gao Y, Zhang F. Drug-induced hypothermia in stroke models: does it always protect? *CNS Neurol Disord Drug Targets* 2013;12:371–380.

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