PERSPECTIVE

Pharmacological induced target temperature management after cardiac arrest: the capsaicinoids

Cardiac or respiratory arrest lasting only a few minutes can inflict grave harm on numerous bodily organs, not least of all, the brain. Neurocognitive deficits, which are often severe and profoundly life altering, remain a major source of morbidity among survivors.

Post-arrest brain injury is extraordinarily difficult to treat. With the exception of anti-seizure medications, there are no approved medications that can be administered either during cardiopulmonary resuscitation or after return of spontaneous circulation, for treating the acute sequelae of post-arrest brain injury. Cardiopulmonary resuscitation, optimal chest compression, and early defibrillation have been increasingly and widely implemented over recent years, thereby improving survival, but as of yet, limited therapeutic intervention is available to reduce post-arrest brain injury.

A recent systematic review of neuroprotective strategies after cardiac arrest identified five pharmaceutical agents and three gases that have been studied in this context (Huang et al., 2014). Pharmaceutical approaches include adenosine and growth factors/hormones including brain-derived neurotrophic factor, insulin-like growth factor-1 and glycine-proline-glutamate, granulocyte colony stimulating factor and estrogen. Medical gases include hydrogen sulfide, hyperbaric oxygen and molecular hydrogen. To date, preclinical studies of the pharmaceutical agents have shown some benefit but overall are inconclusive, while hyperbaric oxygen and molecular hydrogen are said to be promising but not definitively so. Overall, protecting the post-arrest brain has proven to be enormously challenging.

To date, the most promising strategy for neuroprotection in patients with cardiac arrest has been therapeutic hypothermia-target temperature management (TTM). Despite side-effects including pneumonia, sepsis, and stress-related shivering, a recent Cochrane review concluded that conventional cooling to induce mild therapeutic hypothermia improves neurological outcome after out-of-hospital cardiac arrest, compared to no temperature management (Arrich et al., 2016). Conversely, the authors of this comprehensive review found no evidence of benefit for therapeutic hypothermia in patients with in-hospital cardiac arrest, asystole or non-cardiac causes of arrest. Nevertheless, in recent years, TTM has gained rapid and widespread acceptance for treating post-arrest patients. Although the optimal target temperature remains unclear (Nielsen et al., 2013), TTM remains an important feature of post-resuscitation care and is as recommended by international resuscitation guidelines among survivors of cardiac arrest (Aneman et al., 2017).

Targeted temperature management is not straightforward – it requires the use of mechanical devices that are innately cumbersome to implement, and that are not readily adaptable to use outside of a hospital setting. Also, cooling using mechanical devices requires a relatively long time, as a result of which the temperature that is targeted may not be reached until several hours following the ischemic insult (Hypothermia after Cardiac Arrest Study Group, 2002; Nielsen et al., 2013). Moreover, forced hypothermia interrupts normal physiological function and may cause shivering, one of the most common side effects of TTM. These limitations inevitably reduce its widespread use, and likely diminish its overall impact. Thus, investigators have been searching for alternative methods to induce hypothermia, specifically exploring the feasibility of using pharmacological approaches. A recent review summarized the available pharmacological methods for inducing hypothermia, aiming to maintain the TTM and reduce shivering without using paralytic drugs (Choudhary and Jia, 2017). Fast, reversible and safe drug-induced hypothermia that is more manageable than physical hypothermia has become the latest goal in the treatment of post-arrest brain injury.

In 1878, Högyes first observed that the substance responsible for the pungency of red pepper or paprica (capsicum annuum) causes a fall in body temperature when introduced into the stomach of dogs. Nearly 70 years later, in 1947, capsaicin, the purified compound responsible for the pungent activity, was found to produce a deep fall in body temperature when injected intraperitoneally or subcutaneously into mice, rats and guinea pigs. [See (Szolcsányi, 2014) for an excellent historical account.] Another 60 years would pass before this knowledge of capsaicin's hypothermic effect would be exploited for inducing post-arrest hypothermia pharmacologically. This highly important development has been credited to Fosgerau and colleagues, then at the now-defunct biotech company NeuroKey A/S in Denmark (Fosgerau et al., 2010).

It is now known that the capsaicin receptor is transient receptor potential (TRP) vanilloid type 1 (TRPV1), which is expressed constitutively in the peripheral and central nervous systems, and which controls several physiological processes including inflammation, painful sensation, mechanotransduction and thermoregulation. Several members of the TRP superfamily of non-selective cation channels have since been shown to be directly activated by temperature, and hence are known as thermoTRPs (Feketa and Marrelli, 2015). They include warm-sensitive TRPV1, TRPV2, TRPV3, and TRPV4, as well as cold-sensitive TRPM8 and TRPA1.TRPV1 is widely expressed in all tissues and is activated not only by heat (> 43 °C) but also by low pH. TRPM8 also is widely expressed, is the primary molecular transducer of cold somatosensation and, in contrast to TRPV1, is inhibited by acidic conditions. ThermoTRPs are expressed in primary sensory neurons, where they comprise accessible pharmacological targets for controlling body temperature. Pharmacological modulation of TRPV1 and TRPM8 has been shown to produce hypothermia in experimental animals.

In a most timely contribution to this important goal of drug-induced hypothermia, He et al. (2016) investigated the cardiovascular effects and safety of dihydrocapsaicin (DHC), a capsaicin analog that is much more effective than capsaicin in producing hypothermia. Notably, He et al.'s study was carried out in a rodent model of cardiac arrest. Whereas DHC had been shown previously to lower body temperature in healthy mice, rats, cows and monkeys, as well as in a murine model of stroke, DHC had not previously been tested in the context of cardiac arrest. The importance of this experiment lies in the fact that DHC is known to exhibit certain cardiovascular effects – the so-called the Bezold-Jarisch reflex that involves cardiovascular and neurological processes resulting in hypopnea and bradycardia–which could potentially make it unsafe in victims of cardiac arrest. Thus, determining the cardiovascular effects of DHC specifically in a cardiac arrest model is of paramount importance.

In this first study to test the feasibility of DHC-induced hypothermia in treating post-resuscitation rats in an asphyxial-cardiac arrest model, He et al (2016) showed that DHC administered as a constant infusion without bolus steadily decreased body temperature below 34°C within 80 minutes and, after DHC infusion, body temperature was maintained around 34°C for at least 4 more hours. With constant infusion and absent a bolus, there were no notable complications, DHC-treated rats were viable, and their neurological deficit scores were better than controls (He et al., 2016).

The study by He et al. (2016) is a critical milestone that now mandates further, deeper study of DHC in post-arrest neuroprotection. Many experiments can be envisioned, including detailed studies examining effects of DHC on hippocampal pathology, inflammation and cognitive function post-arrest, compared to untreated controls. However, it must be remembered that, in the realm of cardiac and respiratory arrest, physical hypothermia remains the gold standard. Future, head-to-head comparisons between physical hypothermia *vs.* pharmacological treatments, as have been reported in other types of neurological injury (Hosier et al., 2015), will be critical in cardiac arrest models to allow direct comparisons of the safety, ease of administration and short-term as well as long term efficacy of the various treatments. Such studies hold the promise of revealing critical, treatment-related differences not only in outcomes, but also in metabolic responses, inflammatory signaling and gene expression that may well hold the key to future successful translation.

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J. Marc Simard*, Xiaofeng Jia*, Volodymyr Gerzanich
Department of Neurosurgery, University of Maryland School of Medicine, Baltimore, MD, USA (Simard JM, Jia X, Gerzanich V)
Department of Orthopedics, University of Maryland School of Medicine, Baltimore, MD, USA (Jia X)
Department of Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, MD, USA (Jia X)
Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, MD, USA (Jia X)
Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA (Jia X)

***Correspondence to:** *J. Marc Simard, M.D., Ph.D. or Xiaofeng Jia, M.D., Ph.D., msimard@som.umaryland.edu or xjia@som.umaryland.edu.*
***orcid:** 0000-0002-5373-1988 (J. Marc Simard)*
0000-0003-1445-8525 (Xiaofeng Jia)
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