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Is glibenclamide the new cool in CPR?

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The history of cardiopulmonary resuscitation (CPR) for cardiac arrest is a 300-year long story of one major success after another.¹ It was during the Enlightenment, when scholars were attempting to scientifically solve the problem of sudden death, that the various components of CPR—ventilation, circulation, electricity, and organization of emergency medical services—began to take shape. The 19th century gave way to landmark advances in both ventilatory support—intubation innovations and artificial respirators—and in the open- and closed chest circulatory support. More recently, ventricular fibrillation and novel defibrillation techniques were described. In 1960, mouth-to-mouth resuscitation was combined with chest compression and defibrillation. Recent decades have witnessed huge advances in cardiovascular pharmacotherapy that have evolved into the life-saving treatments we now take as routine. Together, innumerable groundbreaking discoveries during the last three centuries have led to the scientific framework for CPR as we know it today. But, since the Enlightenment, CPR has been mostly about the heart, not the brain, whereas arguably, the brain is the organ most vulnerable to cardiac arrest. Only recently have we begun to apply interventions directed specifically at preserving brain function and improving neurological outcome.²

In this issue of CCMED, Kaibin Huang and colleagues³ report their exciting work on neuroprotection in rats after successful resuscitation from 8-minute asphyxial cardiac arrest. In their carefully performed experiments, they found that post-event treatment of surviving rats with glibenclamide substantially improved subsequent survival and neurological outcome. These salutary effects of glibenclamide were associated with reduced neuronal necrosis and apoptosis, as well as diminished inflammation in the hippocampus, the part of the brain generally held to be most vulnerable to ischemia/hypoxia.

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This work by Huang et al. is an important advance in a field that has seen very few. A systematic review published as recently as last year on neuroprotective strategies after cardiac arrest identified only 5 pharmaceutical agents and 3 gases that have been studied in this context.⁴ Sadly, in half of these, efficacy was neutral or negative, underscoring the enormous challenges faced with protecting the brain after cardiac arrest.

To date, the only strategy that has shown promise in providing neuroprotection in patients with cardiac arrest is therapeutic hypothermia.⁵ A recent Cochrane review concluded that conventional cooling methods to induce mild therapeutic hypothermia seem to improve survival and neurologic outcome after cardiac arrest.⁶ As optimal temperatures are clarified, the most exciting frontier for further improvements in neuroresuscitation lies in identifying safe and effective pharmacotherapy for cardiac arrest. In focal cerebral ischemia, the primary aim of intervention has been to restore perfusion. By contrast, in cardiac arrest, cerebral perfusion is often restored rapidly, setting the stage for effective neuroprotection.

The pathophysiology that underlies global cerebral hypoxic ischemia / reperfusion following cardiac arrest is complex, and the molecular mechanisms that are affected by hypothermia are numerous. But, intriguingly, there is a point of apparent convergence—the transcription factor, NF- κ B. It has long been known that NF- κ B is activated during cerebral ischemia / reperfusion, and that mild hypothermia inhibits NF- κ B in experimental stroke,⁷ suppressing the expression of numerous NF- κ B target genes that encode cytokines, adhesion molecules and inducible enzymes such as cyclooxygenase-2, inducible nitric oxide synthase and many others.

The pioneering work of Huang et al. dovetails nicely with the decades-long work on hypothermia. Two genes critical to this story, both of which are upregulated by NF- κ B, are *Abcc8* and *Trpm4*, the genes that encode Sur1 and Trpm4,⁸ which have been closely linked to cerebral ischemia/reperfusion injury. The fact that the *Abcc8* and *Trpm4* genes are regulated by NF- κ B suggests that hypothermia should reduce expression of Sur1-Trpm4 channels. Logically, inhibiting Sur1 with glibenclamide should yield effects similar to those observed with hypothermia. As reported here by Huang et al., Sur1 and Trpm4 protein and mRNA are both increased in the brain after cardiac arrest, and glibenclamide blockade improves survival and neurological outcome, and reduces neuronal necrosis, apoptosis and inflammation—effects that closely parallel those seen with hypothermia.

Have Huang and colleagues given us a glimpse of a specific, critical molecular mechanism—inhibition of the NF- κ B/Sur1-Trpm4 axis—by which hypothermia functions? If so, CPR following cardiac arrest could be poised for yet another major leap forward.

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