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Ischemia/reperfusion injury resistance in hibernators is more than an effect of reduced body temperature or winter season

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Hibernating mammals are resistant to injury following cardiac arrest. The basis of this protection has been proposed to be due to their ability to lower body temperature or metabolic rate in a seasonally-dependent manner. However, recent studies have shown that neither reduced body temperature nor hibernation season are components this protection.

From hot to cold and back again, hibernating mammals are capable of adapting to environmental and physiological challenges. The mechanisms underlying this flexibility, when fully understood, could provide the foundation for human therapeutics for ischemia/ reperfusion injury that occurs during cardiac arrest and hemorrhagic shock. Recently we found that arctic ground squirrels (*Urocitellus parry*ii) resist organ damage and systemic inflammation after global ischemia/reperfusion.[1] This resistance was not dependent on the animals' ability to cool during insult or on hibernation season.

The role that reduced body temperature plays in resistance to ischemia/reperfusion injury in ground squirrels is poorly understood. In non-hibernating mammals, damage from ischemia/reperfusion is diminished when body temperature is lowered by reducing metabolic rate, including the biochemical reactions that form damaging reactive oxygen species and promote inflammation. Therapeutic hypothermia improves neuronal survival in experimental models of ischemia/reperfusion and improves survival and neurological outcome following cardiac arrest.[2] Evidence that the arctic ground squirrel is protected from ischemia/reperfusion without cooling includes studies showing that the arctic ground squirrels' brain is protected from cardiac arrest even when not hibernating and when brain temperature is maintained at 37 °C.[3] Importantly, in prior isolated organ ischemia/reperfusion experiments in other ground squirrel species, the animals were allowed to cool during ischemia and/or reperfusion making it difficult to untangle innate protection from that conferred from the lowered body temperature.

Like temperature, the hibernation season may also enhance ischemia/reperfusion injury resistance by changing the use of metabolic fuels or by preparing the animals to enter a hypometabolic state. As with temperature, the role that hibernation season plays in protection from ischemia/reperfusion injury in ground squirrels remains a matter of debate. It has been shown that seasonal hibernators resist ischemia/reperfusion injury in liver, heart, brain, and small intestine during the hibernation season.[4-6] This protection has been proposed to be influenced by a seasonal switch from carbohydrate (summer) to lipid (winter) metabolism resulting in an increase in ketone bodies, a decrease in lactate formation, and activation of proteins that regulate fuel use such as peroxisome proliferator-activated receptors. Season has also been proposed to alter antioxidant levels, decrease immune function and decrease metabolic rate such as occurs during torpor. Systematic study of ischemia/reperfusion injury in ground squirrels in both summer and winter seasons is lacking, so the seasonal role remains unclear. Without knowing if season is necessary for ischemia/reperfusion injury resistance, it is not possible to determine if seasonal changes in physiology are part of the resistance mechanism.

In our recent study, we challenged arctic ground squirrels with cardiac arrest or hemorrhagic shock. We removed hypothermic effects by maintaining the animals' body temperature at 37.0 ± 0.5 °C during and after ischemia/reperfusion. Even under these conditions, the arctic ground squirrels showed no markers of organ damage, systemic inflammation, or loss of acid/base balance as indicated by a negative base excess. Season also proved to be unimportant in this species' resistance to ischemia/reperfusion injury. Blood chemistries and histopathology showed cardiac arrest and hemorrhagic shock–induced ischemia/reperfusion did not result in organ damage in the active (summer) or hibernation season. In comparison, rats, an ischemia/reperfusion injury-prone species, displayed indications of liver and kidney damage. Rats also had a systemic inflammatory response after ischemia/reperfusion as shown by significant increases in plasma cytokine levels while arctic ground squirrels had no such increases. One possible reason for the lack of ischemia/reperfusion injury in the arctic ground squirrel may be metabolic stability during insult. Base excess comprises the metabolic component of acidosis. During and after ischemia/reperfusion, arctic ground squirrels were able to maintain a positive base excess whereas the base excess in rats became negative. Maintenance of acid/base balance in arctic ground squirrels may be due, in part, to the arctic ground squirrels' ability to use non-glucose energy sources such as free fatty acids or ketone bodies. Although lowered body temperature would be expected to enhance injury resistance observed

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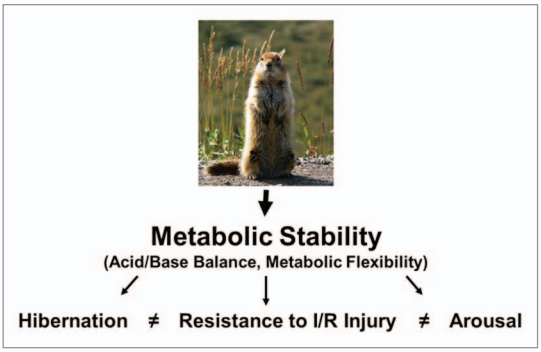

Figure 1. Ischemia/reperfusion injury resistance in arctic ground squirrels is not dependent on low body temperature or hibernation season but is due to metabolic stability defined as acid/base balance and the ability to switch between glucose and lipid energy sources to avoid lactate accumulation (photograph courtesy of Kim Turnball).

in arctic ground squirrel, lowering body temperature was not necessary for arctic ground squirrels to tolerate cardiac arrest or hemorrhagic shock better than rat.

Additionally, we found that the winter season was not necessary for arctic ground squirrels to resist ischemia/reperfusion injury. Arctic ground squirrels challenged with hemorrhagic shock showed no evidence of injury when they were tested in winter or summer. Importantly, we found that summer and winter arctic ground squirrels differed in their metabolic profiles, however these seasonal changes in metabolism were not necessary for ischemia/reperfusion injury resistance.[7] The metabolic fingerprints of summer or winter arctic ground squirrels were not altered in a statistically significant manner after hemorrhagic shock-induced ischemia/reperfusion, whereas the metabolic fingerprint of rat was altered by ischemia/reperfusion. Taken together, the ability for arctic ground squirrels to withstand ischemia/reperfusion insults appears to be due to an innate ability to stabilize metabolism under extreme physiological challenges. How arctic ground squirrels achieve metabolic stability has yet to be determined. They may enjoy metabolic flexibility; i.e., the ability to switch from carbohydrate to fatty fuels in both summer and winter seasons, shunt blood to vital organs, benefit from enhanced pH buffering capacity, or have the ability to decrease metabolic rate when blood flow is decreased, regardless of hibernation season. Why or if other species of ground squirrel resist ischemia/reperfusion injury better during the winter vs. summer season requires further study.

Ischemia/reperfusion injury and subsequent systemic inflammation and organ failure pose serious concerns in human medicine. Species such as the arctic ground squirrel may hold clues into possible interventions to ameliorate damage from ischemia/reperfusion. To date, researchers have explored several of the mechanisms that may contribute to the ability of these animals to tolerate ischemia/reperfusion, including metabolic intermediates, antioxidants, hypothermia, immune system alterations, and the ability of the small intestine to withstand ischemia/reperfusion. Multiple protective mechanisms may contribute to the ability to rewarm from the torpid state without incurring tissue damage. Nonetheless, there is no consensus on what role these factors play in the documented ability of these animals to tolerate ischemia/reperfusion. More likely than not, there is a network of redundant systems insuring that these animals survive and thrive despite multiple iterations of suppressed blood flow followed by rapid return of normal circulation over the course of a hibernation season or during a more human-like event such as cardiac arrest or hemorrhagic shock. Importantly, in arctic ground squirrels, these mechanisms do not depend on decreased body temperature or the winter season.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Bogren LK, et al. PLoS One 2014; 9:e94225; PMID:24728042; http://dx.doi.org/10.1371/journal.pone.0094225
2. Bernard SA, et al. N Engl J Med 2002; 346:557-63; PMID:11856794; http://dx.doi.org/10.1056/NEJMoa003289
3. Dave KR, et al. Stroke 2006; 37:1261-5; PMID:16574920; http://dx.doi.org/10.1161/01.STR.0000217409.60731.38
4. Andrews MT, et al. Am J Physiol Regul Integr Comp Physiol 2009; 296:R383-93; PMID:19052316; http://dx.doi.org/10.1152/ajpregu.90795.2008
5. Carey HV, et al. Physiol Rev 2003; 83:1153-81; PMID:14506303
6. Martin SL, et al. Am J Physiol Regul Integr Comp Physiol 2008; 295:R316-28; PMID:18434441; http://dx.doi.org/10.1152/ajpregu.00418.2007
7. Bogren LK, et al. FASEB J 2014; (Forthcoming)