Editorial

Thank goodness for progress

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In antiquity, the only means by which a medical practitioner could evaluate the body’s glucose state was gustatory examination of the urine. The method accounts for the term “mellitus,” Latin for “honey,” in the description of diabetes. Thankfully, for those who practice in modern times, the science of medicine has progressed significantly. Since Claude Bernard described the “milieu intérieur,” the body’s system of maintaining a stable internal environment, our understanding of endocrinology has grown dramatically. But one thing has become especially clear: the more that is known, the more we have yet to discover.

The relationship between hyperglycemia and poor neurological outcome is well established. What is not certain is whether a causal relationship between the two exists or whether a common process results in both. Further, what happens when glucose levels are manipulated in an attempt to improve neurological outcome? In their article, Zetterling and colleagues describe their experience with intracerebral microdialysis (MD) monitoring over a week in 19 patients who suffered subarachnoid hemorrhage (SAH). The study is important because it focuses on several aspects of cerebral energy utilization after SAH that have not been previously described. These aspects include the effect of systemic glucose levels on cerebral glucose availability, the changes to both after the administration of insulin, and the manner in which these processes evolve over 7 days after the hemorrhage.

The prospective randomized trial of intensive insulin therapy in critically ill patients by Van den Berghe and colleagues in 2001 was a seminal study that changed the practice of critical care across the world. In a rigorous scientific manner, the authors demonstrated significant differences in outcome as a result of tight blood glucose control in a surgical intensive care unit (ICU) population. A similar study of medical ICU patients followed. The Van den Berghe group then looked at the effect of intensive insulin therapy on the nervous system and in patients with primary neurological disorders to address the concerns of those who differentiate patients with neurological diseases from those with other organ pathologies. The group found lower levels of critical illness polyneuropathy and shorter periods of mechanical ventilation. In the subpopulation with brain injury, the therapy decreased intracranial pressure, seizure frequency, and the incidence of diabetes insipidus. It is difficult to refute the statistical power of these studies. Now, however, we must reconsider these findings.

Previously, it was impossible to provide real-time temporal resolution when examining brain metabolism. With the advent of MD, the brain’s energy needs and the process by which the body supplies them can be better elucidated. Authors of previous reports have examined metabolic states following traumatic brain injury. In 2006, Vespa and colleagues studied energy utilization following traumatic brain injury and found significant reductions in cerebral glucose levels after intensive insulin therapy. While the global metabolic rate did not decrease, glutamate levels, the lactate/pyruvate ratio, and oxygen extraction (all markers of cellular metabolic stress) were elevated. Interestingly, no difference in the 6-month mortality rate was noted. In 20 patients with stroke or traumatic brain injury, Oddo and colleagues similarly found a higher rate of cerebral hypoglycemia and energy crisis with intensive insulin therapy. This increased rate correlated with decreases in systemic glucose. These authors also discerned a greater frequency of cerebral hypoglycemia in nonsurvivors. Looking specifically at patients with SAH, Schlenk and colleagues used MD to examine cerebral metabolism up to 12 hours after initiating insulin infusion. They, too, found cerebral hypoglycemia in a large number of patients but also detected hypoglycemia in some of the patients who did not require insulin, demonstrating that glucose metabolism probably plays a crucial role in this process.

The study by Zetterling and colleagues contributes to the literature in several ways. First, it follows the biochemical changes in the brain that occur in the first 7 days after SAH. It is not surprising that the metabolic activity of the brain evolves with time as it attempts to reestablish function after an insult. In the study, there was a progressive decrease in cerebral glucose levels despite relatively constant plasma glucose concentrations. Also present was a decrease in glutamate as well as elevations in both pyruvate and lactate. In the absence of signs of cellular stress, these changes indicate an increase in energy consumption following the hemorrhage.

Second, the study shows the complex relationship between energy needs and energy delivery. Numerous factors influence the energy state of the brain, including systemic glucose levels, blood-brain barrier integrity, the number and function of glucose transporters, the need for glucose to maintain normal functions in the brain, and the attempt to limit or reverse injury from the SAH. Of note, the correlation between brain and plasma glucose improved with time in the current study, potentially indicating a normalization of some of these mechanisms. Unfortunately, it is nearly impossible to isolate a single portion of this process to examine it in human patients.
Finally, the authors examine the effects of exogenous manipulation of the system in the form of insulin administration. Insulin did cause cerebral hypoglycemia, as observed in other reports. However, the lactate/pyruvate ratio remained unchanged, indicating an alteration of glucose utilization rather than energy crisis.

As our understanding of regulatory mechanisms and their response to pathological conditions grows, so does our ability to improve patient care and outcomes. The authors of this study are to be congratulated for their efforts to elucidate the complexities of energy regulation in response to severe brain injury. May the fruits of their labors taste sweet as their discoveries continue to grow.

**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**References**


**Response**

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First, we commend the authors on their illuminating introductory history lesson. Second, we reaffirm that the relationship between plasma and brain glucose is still unclear, particularly as it relates to cerebral energy metabolism, cellular energy crisis, and brain injury. The cerebral metabolic response to reductions in plasma glucose can result in different neurochemical MD patterns. As we found in our study, one such pattern is insulin treatment reducing extracellular brain glucose and pyruvate without a resultant increase in cellular distress markers, that is, MD lactate/pyruvate ratio, glutamate, and glycerol. In this case the tested tissue may not be compromised, and outcome should not be affected. However, if cerebral energy metabolic demand increases, there is the risk of a more profound energy perturbation with signs of cellular distress, potentially affecting tissue outcome. In our study, we did not address outcome in relation to MD glucose levels given the small size of our patient sample. However, we emphasize that MD provides regional biomarker information data from one MD catheter, and thus, the data may not be representative of the entire human brain. This fact may explain differences in outcome among studies of similar insulin treatment regimens. Despite this methodological limitation, our data clearly showed that the administration of insulin was related to decreases in MD glucose and MD pyruvate, often to critically low levels, even though plasma glucose values remained above 6 mmol/L. This finding supports the notion that tight blood glucose control should be avoided in patients with acute brain injury. In addition, our results suggest that later after SAH, brain energy metabolism can switch gears into a hyperglycolytic state with increased glucose and energy demand to repair the injured brain, posing an even greater risk of brain glucose depletion during tight glycemic control.

Finally, the complexity of energy metabolic perturbation following acute human brain injury is increasingly recognized. A concept of nonischemic energy metabolic crisis is emerging and is based on findings that energy metabolic crisis without hypoxia/ischemia appears to be a common phenomenon following TBI. Such an energy crisis may lead to increased excitotoxicity following SAH because of energy shortage and reduced glutamate-glutamine cycle activity. The recent demonstrations of cortical spreading depression as a common feature of acute human brain injury as well as the documented increased shunting of brain glucose to competing pathways, such as the pentose phosphate pathway important for oxidative stress defence and macromolecular synthesis, add to the picture of adverse secondary events posing a risk for the depletion of brain glucose in the acutely injured human brain.

Even though available data already suggest that low brain glucose may be related to poor outcome, much research is still needed to improve our knowledge of the complex energy metabolic perturbations in acute human brain injury and how such knowledge translates into clinical practice.

**References**

1. Cesarini KG, Enblad P, Ronne-Engstrom E, Marklund N, Sal-