Cerebral Metabolism and the Role of Glucose Control in Acute Traumatic Brain Injury

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KEYWORDS

• Traumatic brain injury • Glucose control • Metabolism • Neurovascular unit • Metabolic crisis • Outcome • Hyperglycolysis • Cerebral microdialysis

KEY POINTS

- Hyperglycemia is often observed in critical illness and severe TBIs, indicating systemic physiologic stress and severity of injury.
- Acute hyperglycemia has been found to be associated significantly with poor functional outcome and high mortality in severe TBI.
- Randomized clinical trials addressing hyperglycemia so far have failed to demonstrate improvement in neurologic outcomes after severe TBI, prompting further research to understand the disease process.
- Recent advancements in preclinical and clinical research shift the focus to the physiology of glucose use at the neurovascular unit level in the brain, where glucose metabolism is altered.
- Future research will shed light into the promise of alternative energy delivery methods.

INTRODUCTION

The human brain consumes about 25% of cardiac output, reflecting the high energetic demand that brain cells depend on to function at physiologic conditions. Energy demand and use are dramatically altered following severe traumatic brain injury (TBI) creating a biologic dilemma for neuronal survival and functional preservation.

Despite significant advances in the understanding of brain physiology and evidence demonstrating that blood flow regulation and oxygen delivery optimization improve the chances of survival after TBI, the most up-to-date Brain Trauma Foundation management guidelines do not include a formal recommendation in regards to systemic glucose control or brain glucose optimization.[1] Yet, mounting scientific experimental and clinical evidence demonstrate that systemic glucose derangements and deviation from a physiologic cerebral glucose metabolism further exert a negative impact in recovery from TBI, by exacerbating secondary tissue injury, hindering functional outcomes, and increasing the chance of mortality.

According to the Centers for Disease Control and Prevention, 2.2 million patients visit emergency rooms each year for TBI in the United States alone. Of those, about 250,000 are hospitalized and about 50,000 die as a result of their injury

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(http://www.cdc.gov/traumaticbraininjury/data/). Improved protocols exist for management of intracranial pressure (ICP), cerebral perfusion pressure, and brain oxygenation. However, despite increased knowledge and understanding about glucose metabolism at the systemic level and in the brain, clinical trials aimed at controlling systemic hyperglycemia have failed to improve neurologic outcomes and survival after TBI. In a general critical care patient population, results have shown higher mortality with the intensive insulin therapy (IIT) strategy to control elevated serum glucose. In the neurologic population that suffers from severe TBI the results have been equally disappointing.

A thorough review of the pathophysiologic mechanisms behind cerebral metabolic failure supported by current scientific evidence and an outline toward future directions in management and research are discussed.

BRAIN GLUCOSE METABOLISM PRINCIPLES

Glycolysis is perhaps one the most preserved biologic processes from prokaryotes to mammals consisting of the biochemical steps that allow glucose use as a source of energy.[2–4] It occurs in the cytoplasm and results in production of pyruvate, lactate, and ATP. Pyruvate then diffuses across cellular compartments to reach the mitochondria where it is prepared to enter the citric acid cycle (Krebs cycle) in the form of acetyl-CoA. The end result is further generation of ATP, CO_2, and nicotinamide adenine dinucleotide. Nicotinamide adenine dinucleotide then enters the electron transport chain and through oxidative phosphorylation results in the production of large amounts of ATP. Oxygen is consumed as the electron acceptor allowing restoration of NAD^+ to maintain the cycle. This well-defined pathway constitutes aerobic respiration (**Fig. 1**).

The Krebs cycle is not only crucial for generation of chemical energy, but also to provide the cell with the necessary precursor materials to synthesize some amino acids, and in the case of neurons, neurotransmitters. Not all pyruvate generated by glycolysis enters the Krebs cycle; about 15% of pyruvate is converted to lactate, which in turn can be used to generate energy. Under anaerobic

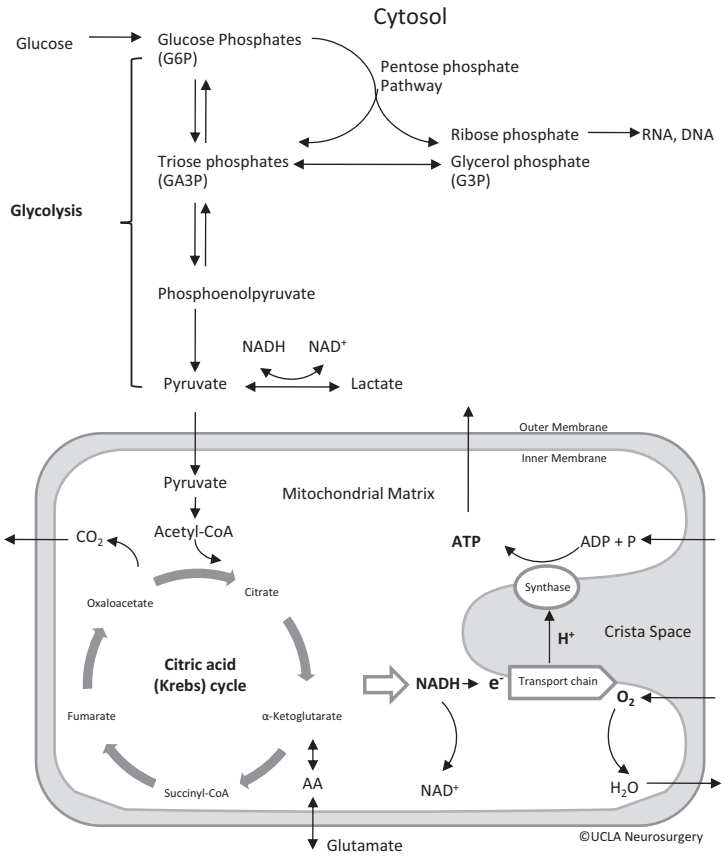

Fig. 1. Simplified diagram of glycolysis, citric acid cycle, and cellular respiration. All enzymes necessary for the glycolytic pathway are present in the cytosol allowing the metabolism of glucose into pyruvate and lactate. Pyruvate enters the mitochondrial matrix via a proton symporter where it is irreversibly oxidized to aceyl-CoA, the main substrate of the tricarboxylic (citric acid or Krebs) cycle. This cycle is important in the reduction of coenzymes necessary for the cellular respiration and other cellular processes. Cellular respiration occurs at the mitochondrial cristae with the end result of net production of 38-mol ATP (oxidative phosphorylation) for cellular energy use. Alternatively, lactate is the end product of glycolysis under anaerobic conditions leading to a net result of 2-mol ATP. AA, aminoacid; acetyl-CoA, acetyl coenzyme A; e^-, electron; G3P, glycerol 3-phosphate; G6P, glucose 6-phosphate; GA3P, glyceraldehyde 3-phosphate; NAD^+/NADH, nicotinamide adenine dinucleotide; P, phosphate. (*Courtesy of* Dr Manuel M. Buitrago Blanco, MD, PhD, Department of Neurosurgery, Neurological ICU, University of California, Los Angeles, 2016.)