Restoring Energy Deficits in Traumatic Brain Injuries: A Key to Effective Treatment

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Restoring Energy Deficits in Traumatic Brain Injuries: A Key to Effective Treatment

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I. Background

- Traumatic brain injury (TBI) is a leading cause of death and disability. \textsuperscript{1}
- Developing treatments that would help TBI patients recover faster and more completely would reduce healthcare costs, benefit society, and improve the quality of life for TBI victims.
- The path to developing better TBI treatments involves understanding the underlying mechanisms of the brain’s response to TBI.

II. Objectives

- Explain TBI pathophysiology.
- Examine the role of ketones in TBI.
- Identify potential future approaches to using ketones as a treatment for TBI.

III. TBI Pathophysiology

Primary Injury Mechanisms \textsuperscript{2}
- Biomechanical Damage
- Injury to nervous tissue structures
- Mechanical stress/deformation
- Stretching, compressing, and tearing of cells

Secondary Injury Mechanisms \textsuperscript{2}
- Cascade of pathological consequences
- Exotoxicity
- Calcium overload
- Impaired glucose metabolism
- Oxidative stress
- Mitochondrial dysfunction
- Inflammation

Time: microseconds \( \rightarrow \) seconds

Injury to nervous tissue structures

Post Traumatic Energy Crisis

Ketone Metabolism and TBI \textsuperscript{5}

IV. Post Traumatic Energy Crisis and Ketones

Ketones and the Mitochondrial Permeability Transition Pore \textsuperscript{6}
- When Ca\textsuperscript{2+} homeostasis fails through trauma induced Ca\textsuperscript{2+} overload, the mitochondrial permeability transition pore (mPTP) opens, which further increases energy deficits.
- Ketones can function in the same way as Cyclosporine A, an immunosuppressant drug, that has been shown to be associated with mPTP closure.
- mPTP closure can help restore ionic balance and coupling of mitochondrial oxidative phosphorylation to ATP production.

Post Traumatic Energy Crisis \textsuperscript{3}
- The consequences of secondary injury mechanisms result in cerebral energy deficits.
- The magnitude of cerebral energy deficits is the best prognostic indicator for TBI outcomes.

Endogenous Ketones \textsuperscript{4}
- Ketone bodies are produced from the breakdown of fatty acids in conditions of low glucose.
- In ketosis, the ketone body, \( \beta \)-hydroxybutyrate, can cross the blood brain barrier and be used as fuel.
- Ketone bodies are more metabolically efficient than glucose.

Ketone Action Sites (black diamonds)
- A. 3 enzymatic steps to enter TCA cycle
- B. Reduce NAD couple, which decreases mitochondrial free radical production
- C. Increase energy of ATP
- D. Increase glutathione peroxidase activity, decreasing cystolic free radicals

TBI Actions (white diamonds)
- 1. Decrease in glucose uptake
- 2. Decrease in glycolytic processing of glucose
- 3. Increase glucose use by pentose phosphate pathway
- 4. Decrease ATP production
- 5. Increased oxidative damage to proteins, lipids, DNA

V. Current Research

- Several animal models have shown that TBI recovery improves when ketosis is achieved through fasting, ketogenic diets, and exogenous ketone administration. \textsuperscript{1,4}
- Clinical trials are currently investigating the effect of ketogenic diets in severe TBI. \textsuperscript{7}
- Achieving ketosis through a ketogenic diet requires several days. This time frame may not be practical for the most effective TBI treatment.

VI. Exogenous Ketones

- Exogenous ketones can be administered to immediately raise blood ketone concentrations to therapeutic levels. \textsuperscript{5}
- No human studies have evaluated the effectiveness of exogenous ketones in TBI treatment.
- There are several methods of exogenous ketone administration, each with benefits, limitations, and unknowns. \textsuperscript{6}

VII. Future Perspectives

- Given the lack of targeted pharmacological therapies for TBI, exogenous ketone therapy may provide significant benefit.
- Unanswered questions remain about dosing, timing, and the route and duration of exogenous ketone administration.
- Larger studies with more robust neuroimaging and functional outcome endpoints are needed. \textsuperscript{8}

VIII. References