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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. ref. 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

Traumatic Insult

Primary Injury Mechanisms ref. 2
- Biomechanical Damage
- Injury to neuro-axonal structures
- Mechanical stress/deformation
- Stretching, compressing, and tearing of cells

Time: *microseconds → seconds*

Secondary Injury Mechanisms ref. 2
- Cascade of pathological consequences
- Excitotoxicity
- Calcium overload
- Impaired glucose metabolism
- Oxidative stress
- Mitochondrial dysfunction
- Inflammation

Time: *minutes → weeks*

= **Post Traumatic Energy Crisis**

Neuropathologies ref. 2
- Neurodegeneration
- Cognitive dysfunction
- Neuropsychiatric
- Comorbidities

Time: *weeks → years*

IV. Post Traumatic Energy Crisis and Ketones

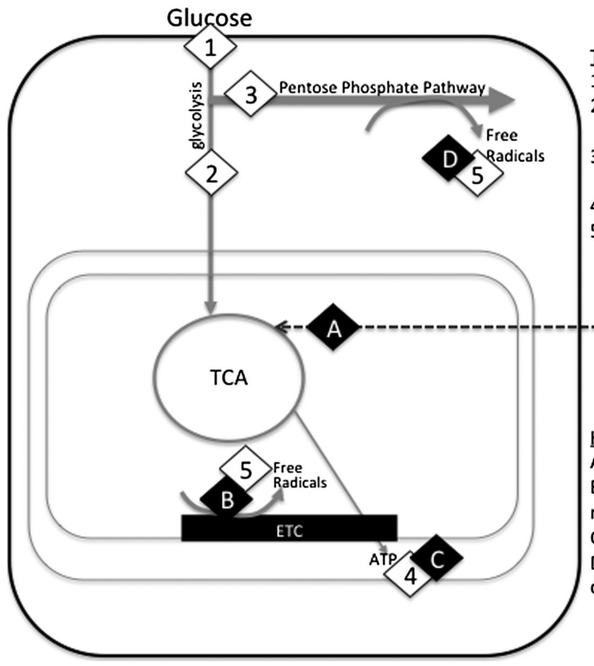
Post Traumatic Energy Crisis ref. 3

- 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 ref. 4

- Ketone bodies are produced from the breakdown of fatty acids in conditions of low glucose.
- In ketosis, the ketone body, **β-hydroxybutyrate**, can cross the blood brain barrier and be used as fuel.
- Ketone bodies are more metabolically efficient than glucose.

Ketone Metabolism and TBI ref. 5

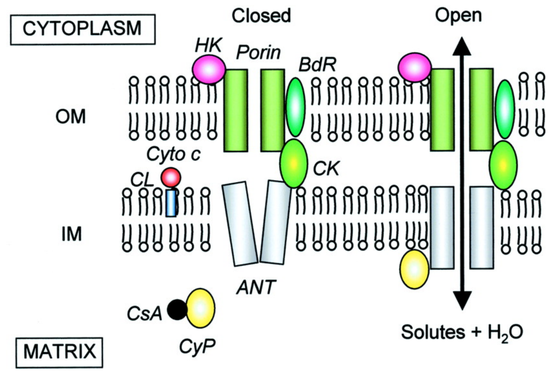


TBI Actions (white diamonds)
1. Decrease in glucose uptake
2. Decrease in glycolytic processing of glucose
3. Increase glucose use by pentose phosphate pathway
4. Decrease ATP production
5. Increased oxidative damage to proteins, lipids, DNA

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 cytosolic free radicals

Ketones and the Mitochondrial Permeability Transition Pore ref. 6

- When Ca^{2+} homeostasis fails through trauma induced Ca^{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 show to bind to the pore complex and induce mPTP closure.
- mPTP closure can help restore ionic balance and coupling of mitochondrial oxidative phosphorylation to ATP production.



V. Current Research

- Several animal models have shown that TBI recovery improves when ketosis is achieved through fasting, ketogenic diets, and exogenous ketone administration. ref. 4
- Clinical trials are currently investigating the effect of ketogenic diets in severe TBI. ref. 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. ref. 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. ref. 8

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. ref. 8

VIII. References

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