Ketones Inhibit Mitochondrial Production of Reactive Oxygen Species Production Following Glutamate Excitotoxicity by Increasing NADH Oxidization


Presentation by Joey Miller
Neuroprotection

What is glutamate excitotoxicity?

- Implicated in stroke, epilepsy, trauma, Alzheimer’s disease
- Associated with higher cellular levels of Reactive Oxygen Species (ROS)

Maalouf et. al (2007)

- Studied effects of two ketone bodies on excitotoxicity
  - Beta-hydroxybutyrate (BHB)
    - Prevents death of hippocampal neurons exposed to amyloid plaque
    - Reduces brain injury due to ischemia
  - Acetoacetate (ACA)
    - Protects hippocampal neurons against glycolysis inhibition
    - Acetone
      - Not physiologically relevant, excluded from study

Ketones Reduce Neuronal Swelling and Death

- Neurons incubated with PI, exposed to 10 uM glutamate:
  - 6/12 displayed PI
- BHB and ACA applied, 1 mM each:
  - 0/10 displayed PI

Why?

No observed morphological changes; no significant measurable changes in surface area

DHE fluorescence reflects superoxide radical levels. 1 mM each of BHB and ACA.

Conclusion: Radical count is reduced. What is the mechanism?
MCB fluorescence reflects levels of active glutathione, an endogenous antioxidant. **Conclusion:** Activity is consistent with KB acting independently of glutathione to prevent ROS buildup.

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### Study of NAD(P)H autofluorescence.

Higher levels of NADH are associated with increases in free radical production; oxidation of NADH results in reduction of ROS.

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Recall: Glutamate excitotoxicity causes Ca²⁺ to leak into mitochondria which increases ROS. Rhod-2 is an indicator of mitochondrial Ca²⁺.

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**Effects on Isolated Mitochondria**

KB reduces effects of Ca²⁺ (0.5 mM) on both ROS and NADH back to baseline.

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**Summary**

- Oxidative stress occurs during glutamate excitotoxicity and damages biomolecules, contributes to energy failure, and can cause apoptosis.
- Ketones prevent glutamate excitotoxicity by reducing ROS without altering glutathione levels.
- This occurs through enhanced NADH oxidation and mitochondrial respiration.
Other research has implicated ketones as causing the effects of calorie restriction...

D-beta-hydroxybutyrate protects neurons in models of Alzheimer’s and Parkinson’s disease.

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Abstract

The neuro analogue 1-methyl-4-phenylpyridinium (MPP+), both in vivo and in vitro, produces death of dopaminergic substantia nigra cells by inhibiting the mitochondrial NADH dehydrogenase enzyme.

Role of glucose and ketone bodies in the metabolic control of experimental brain cancer

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