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Biol 3230

Imaging brain glucose metabolism in vivo reveals propionate as a major anaplerotic substrate in pyruvate dehydrogenase deficiency

INTRODUCTION

PYRUVATE DEHYDROGENASE (PDH):
- Essential metabolic enzyme.
- Converts pyruvate, product of glycolysis, to acetyl CoA, entry point for the Krebs cycle (Figure 1.).

PYRURUVATE DEHYDROGENASE DEFICIENCY (PDHD):
- Caused by mutation on X chromosome.
- Neurodegenerative disease that can be fatal.
- Glycolysis occurs mostly in muscle and brain tissues, so lactate builds up in brain from pyruvate fermentation.
- Non-functional PDH cannot convert pyruvate to acetyl-CoA and introduction to the Krebs cycle does not occur.

PROPIONATE:
- Substrate that enters Krebs cycle through succinyl-CoA between α-ketoglutarate and succinate.
- Crosses blood brain barrier through monocarboxylate transporters.
- Produced from bacterial anaerobic fermentation of resistant starch.

DISSCUSSION

- First time propionate metabolism in the brain *in vivo* was reported (Figure 2.).
- Glutamine is synthesized in glial cells, so site of propionate metabolism is glial cells and propionate metabolism increased in PDHD brain.
- Increased ^{13}C labeling in propionyl-CoA and methylmalonyl-CoA after introduction of U-^{13}C propionate supports hypothesis that propionate is an anaplerotic substrate in PDHD individuals.
- Increased expression of genes encoding for enzymes involved in propionate metabolism also supports hypothesis.
- Future research for ketogenic diet supplemented with sodium propionate as a possible treatment for PDHD individuals.

AIMS AND HYPOTHESIS

AIM:
- Elucidate how *in vivo* metabolic profile in the brain changes with disease progression and mechanisms behind those changes by using model system of PDHD in mice.
- To resolve propionate metabolism in the brain *in vivo*.

HYPOTHESIS:
- Alternative substrates bypass PDH and are utilized to sustain the Krebs cycle in PDHD brain.
- Propionate is an essential precursor to succinyl CoA in the PDHD brain.

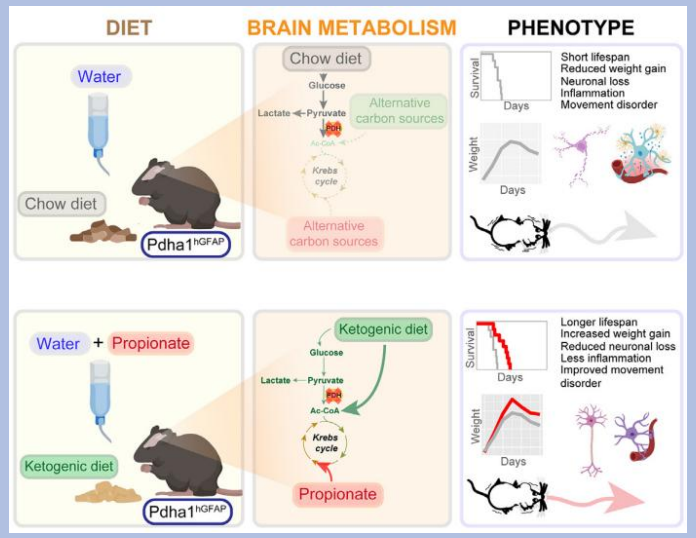

Figure 3. Effects of ketogenic diet with sodium propionate on brain metabolism and mice phenotype compared to control.

METHODOLOGY

ETHICS: All experiments involving mice were approved by animal care and use committees.

PROPIONATE METABOLISM:
- U-13C propionate injected intraperitoneally (0.5 mg/g body weight) to control and PDHD mice at postnatal day 23 after 5 hr fasting period.
- After 30 min several regions of the brain collected.
- Metabolic compartmentation analysis by ^{13}C –NMR isotope distribution analysis.
- Performed analysis of gene expression levels for enzymes involved in propionate metabolism.
- Fed PDHD mice a ketogenic diet with sodium propionate to test therapeutic effects.
- R programming language used for statistical analysis.

RESULTS

- Glucose uptake and metabolism increased in PDHD brain *in vivo*.
- ^{13}C-NMR data showed increased signal of glutamine metabolite in PDHD brain compared to control.
- Propionate primarily metabolized in glial cells in PDHD brain.
- Propionyl-CoA and methylmalonyl-CoA had significantly higher levels of ^{13}C labeling in PDHD mice than controls.
- Significant increase in expression of genes coding for enzymes involved in propionate metabolism.
- Mice on ketogenic diet with sodium propionate showed increased weight gain and reduced neuropathic effects of PDHD. (Figure 3).

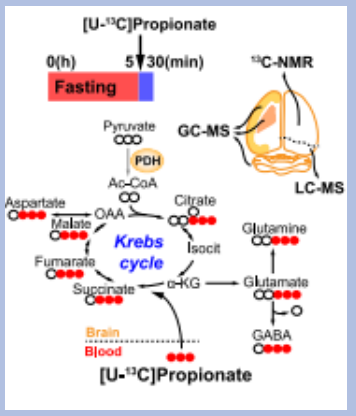

Figure 1. Graphic of experimental methods and Krebs Cycle.

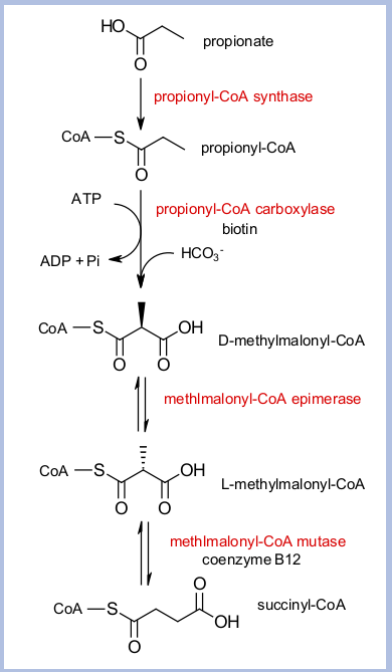

Figure 2. Metabolic pathway of propionate in the brain (Chemdoodle).

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Wongkittichote, P., Ah Mew, N., & Chapman, K. A. (2017). Propionyl-CoA carboxylase - A review. *Molecular genetics and metabolism*, *122*(4), 145–152. https://doi.org/10.1016/j.ymgme.2017.10.002.
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