Acyl-Coenzyme A Thioesters for Pesticides, Parkinson's, and Metabolism

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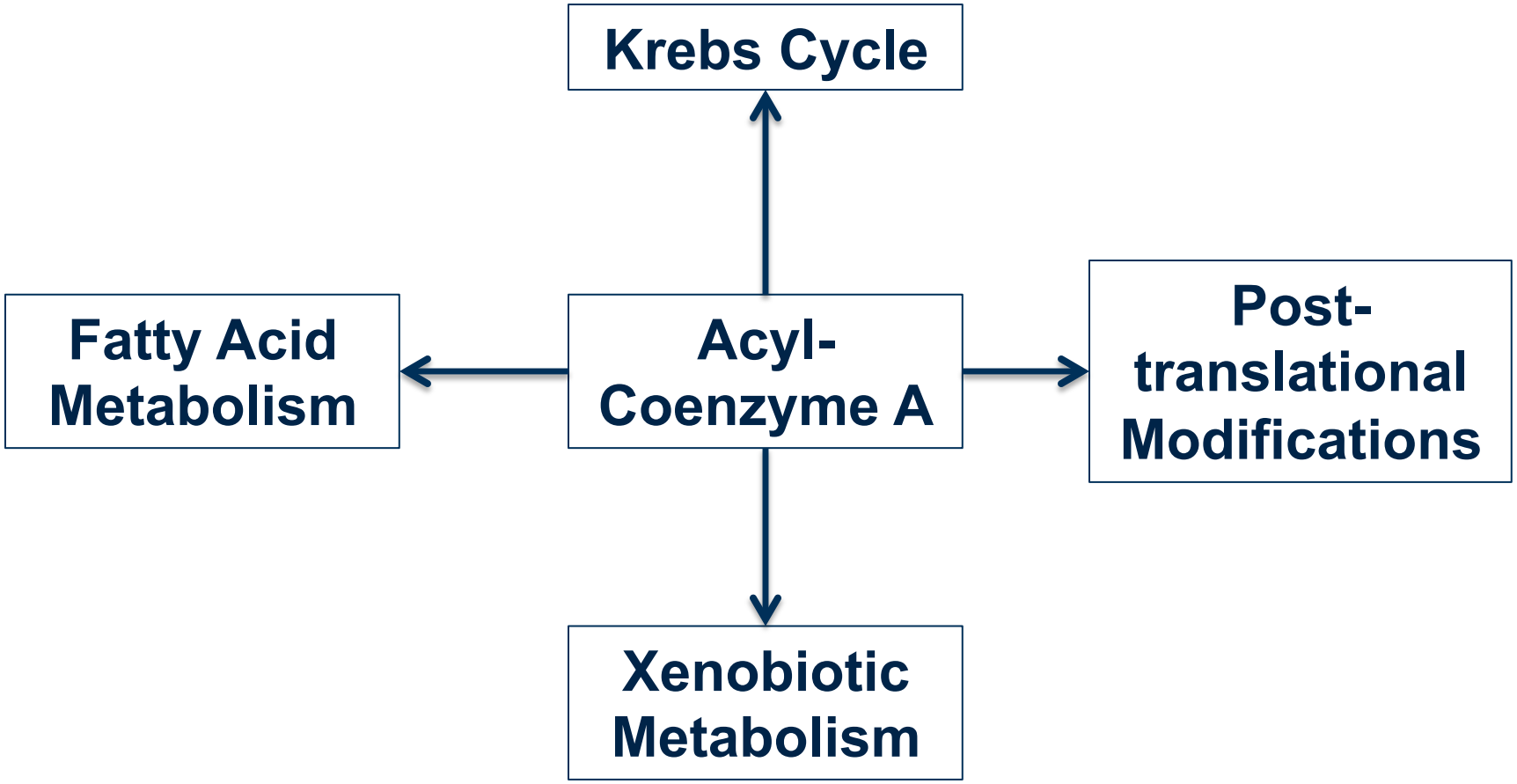
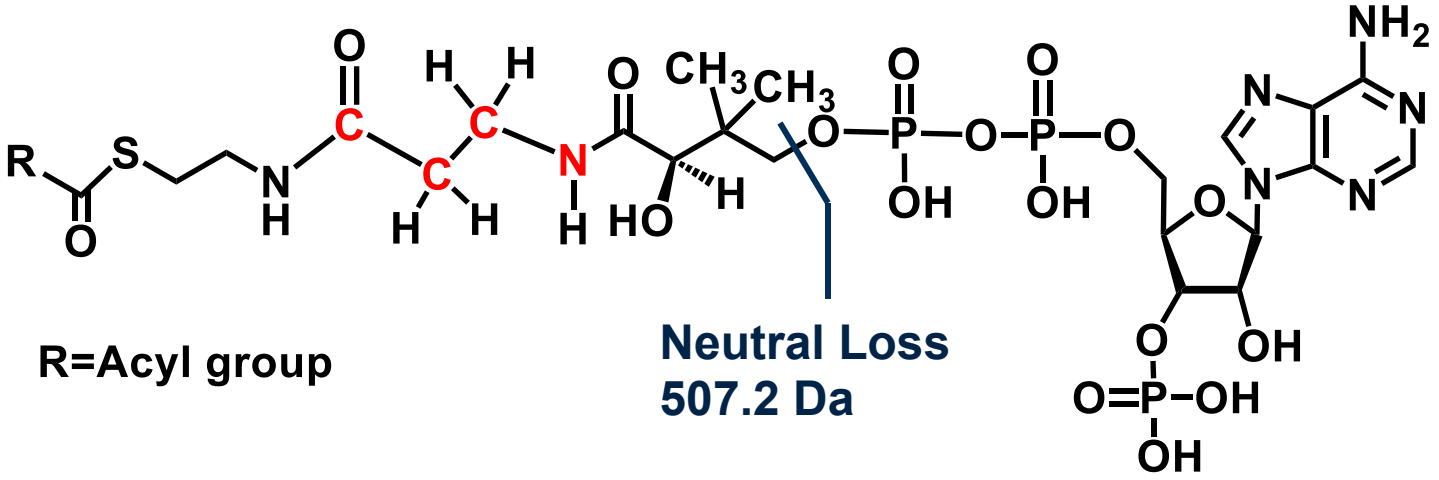
Biological Importance of Acyl-CoAs



MS/MS of Acyl-Coenzyme A Thioesters



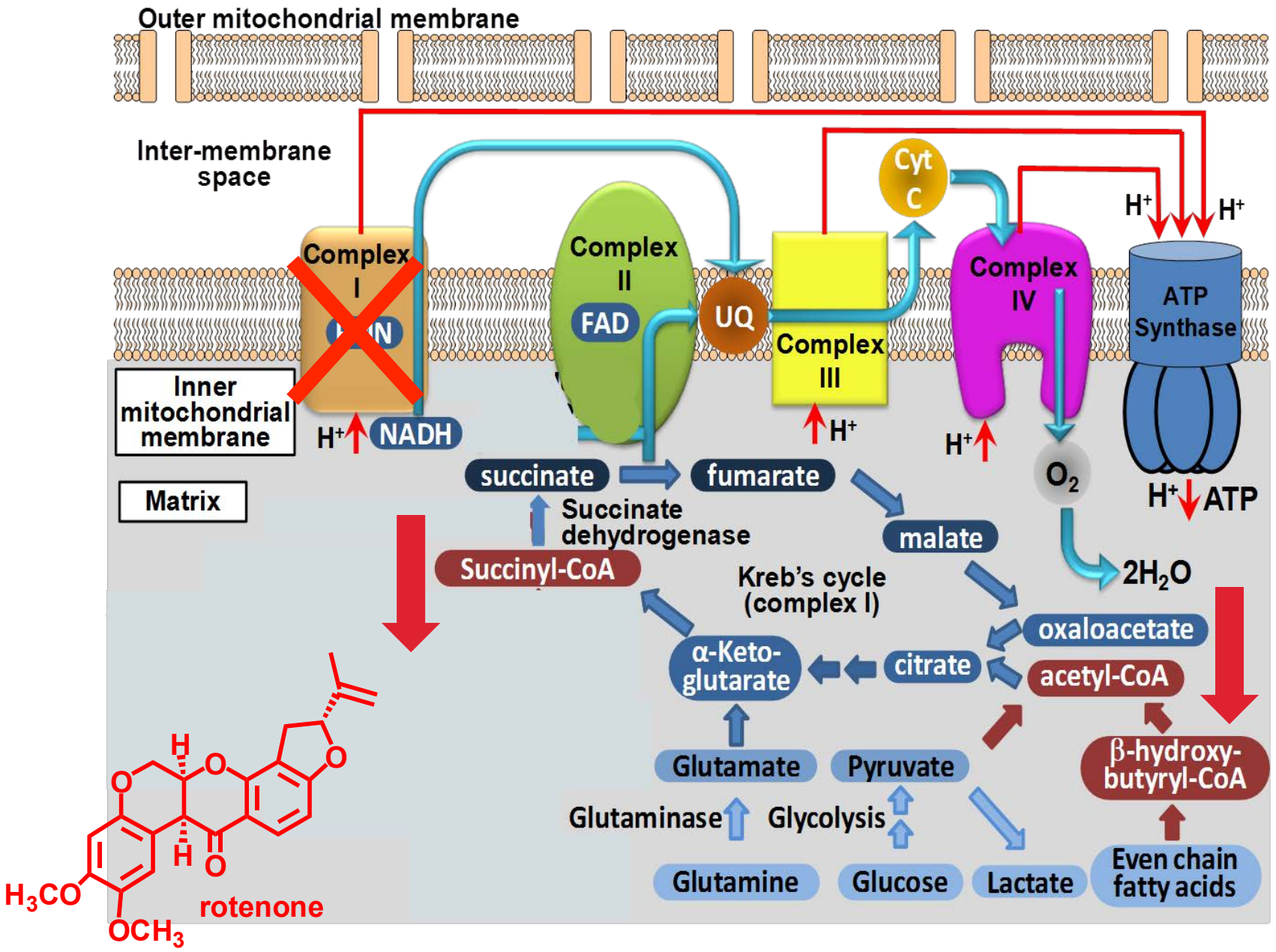
Snyder, *et al*. ***RCM***. 2014, Basu, *et al*. ***Anal. Chem***. 2011, Snyder, *et al*. In Preparation

Rotenone and Parkinson's Disease

- **Rotenone**
  - Widely used pesticide (before 2007)
    - Decades of laboratory/animal studies on toxicity
    - Hypothesized similarity to 1-methyl-4-phenylpyridinium (MPP+) and precursor MPTP
  - Exposure associated with Parkinson's disease
    - Agricultural Health Study
    - Farming and Movement Evaluation
  - 110 PD cases (confirmed by two neurologist consensus)
  - 358 age, sex, state matched controls
  - PD associated with rotenone exposure OR = 2.5 (1.3-4.7)

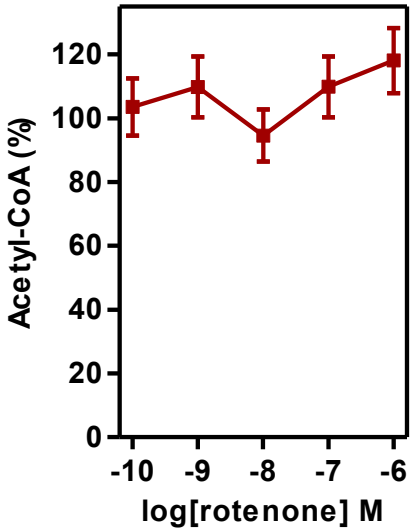
Tanner *et al*. ***EHP***. 2011

Rotenone and Metabolism

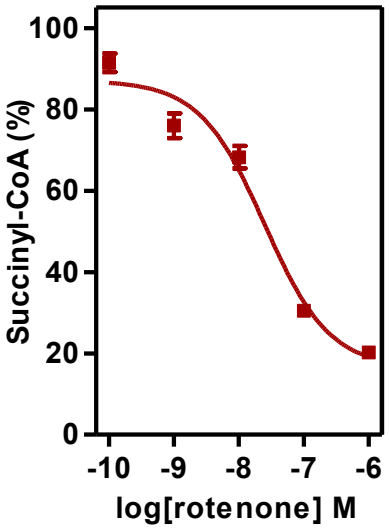


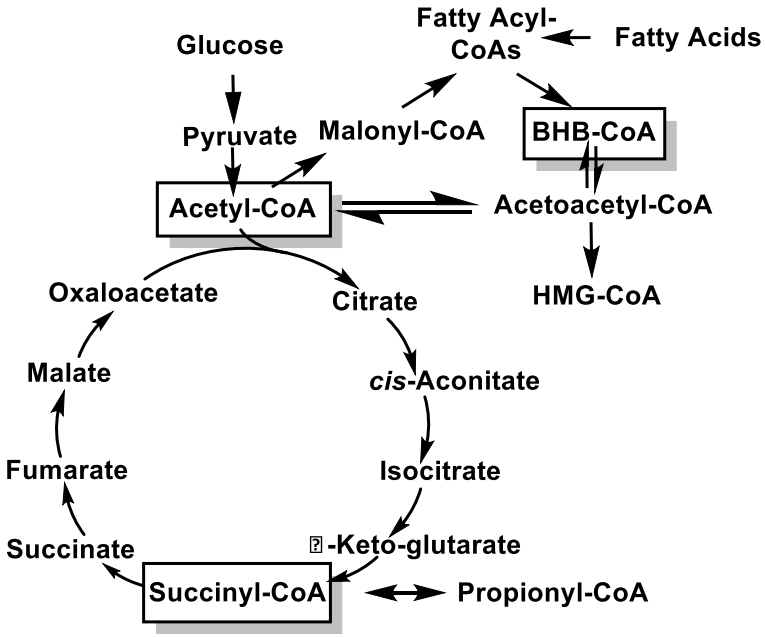
Rotenone Alters Short Chain Acyl-CoA Levels

Acetyl-CoA

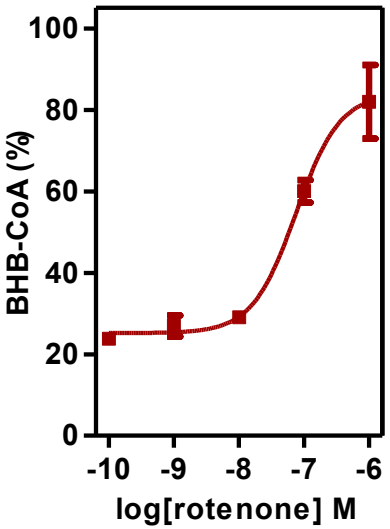


Succinyl-CoA



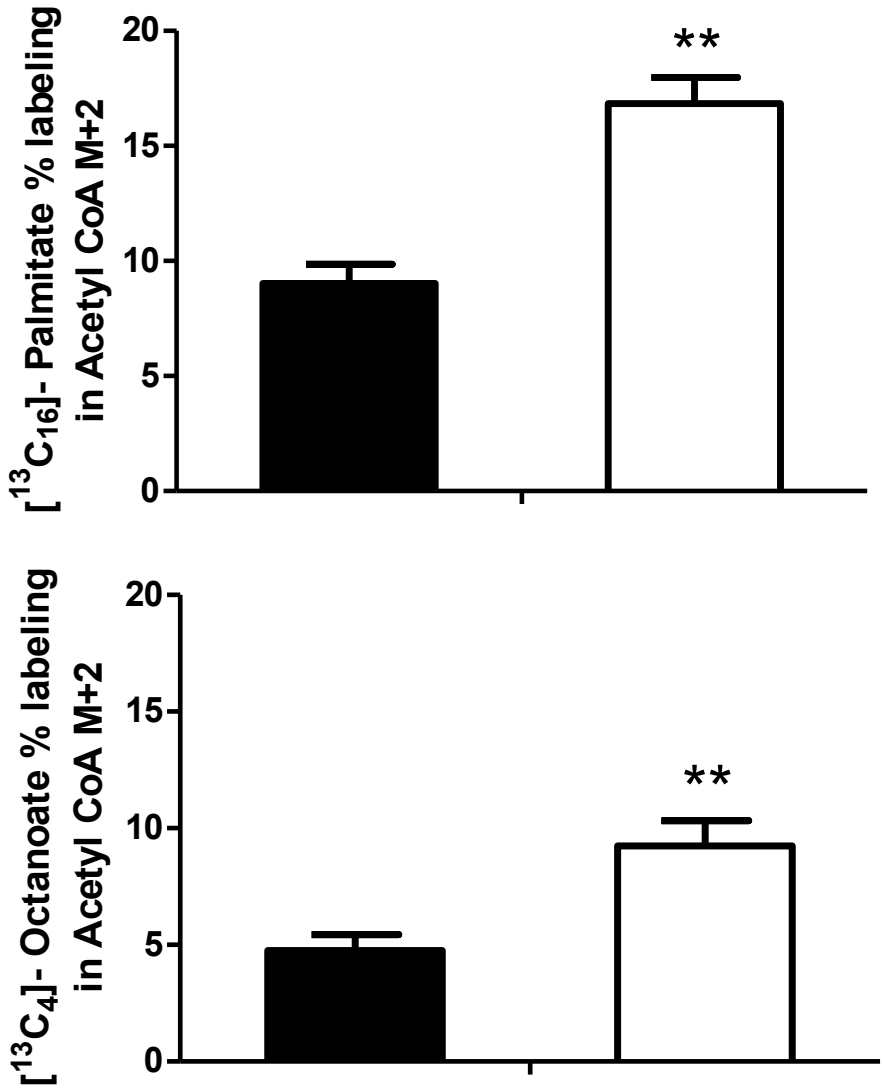


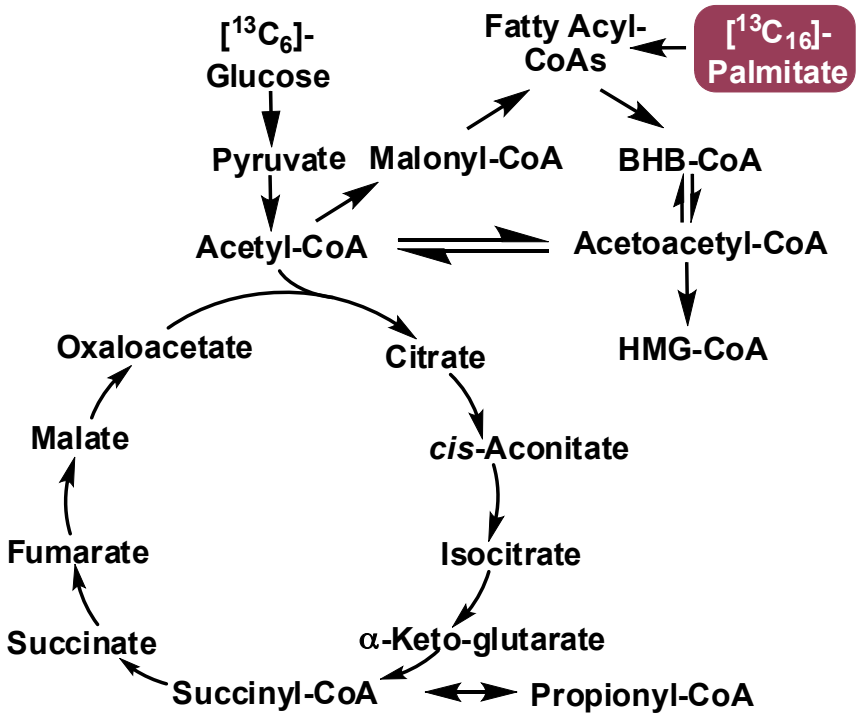
βHB-CoA



Basu, *et al*. ***Chemical Research in Toxicology***. 2011

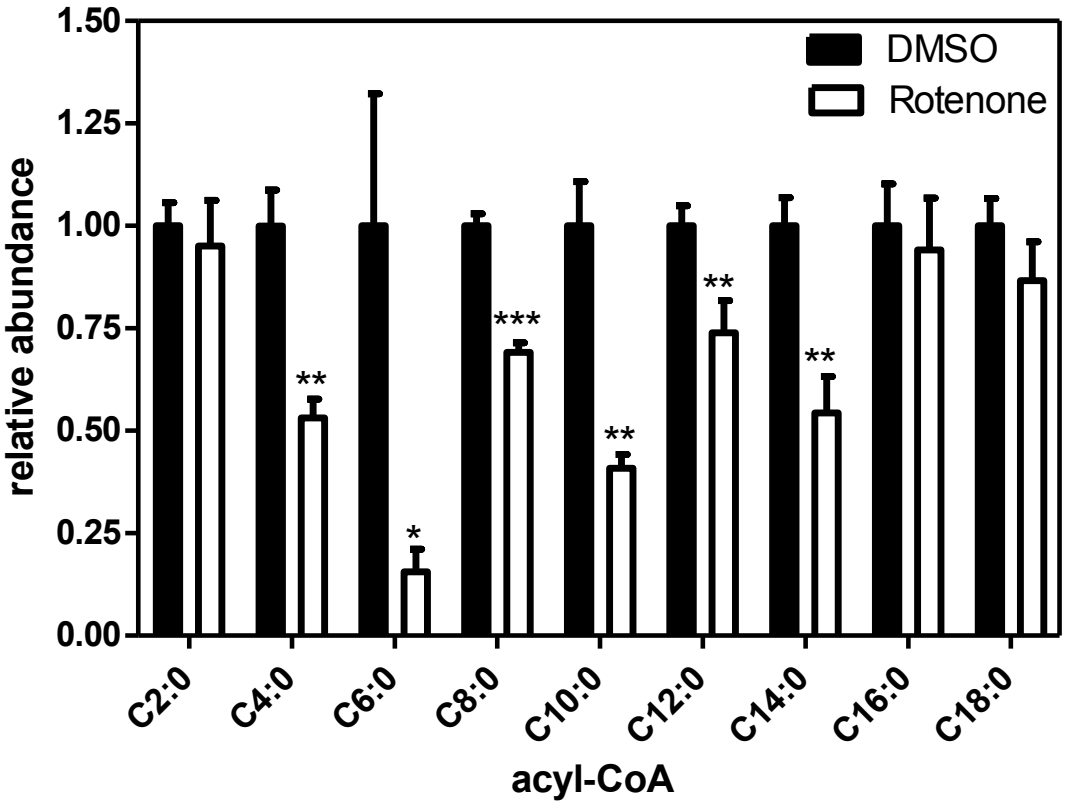
Rotenone Alters Fatty Acid Metabolism



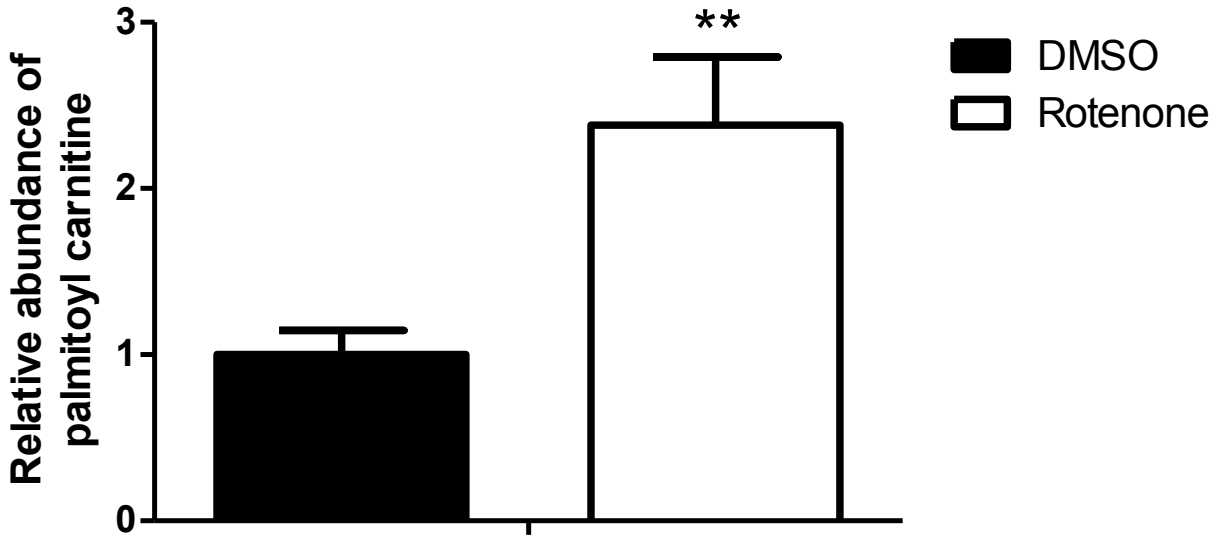


Worth, *et al*. In Review **JBC**. 2014 (see poster TOXI:58. Tu Evening)

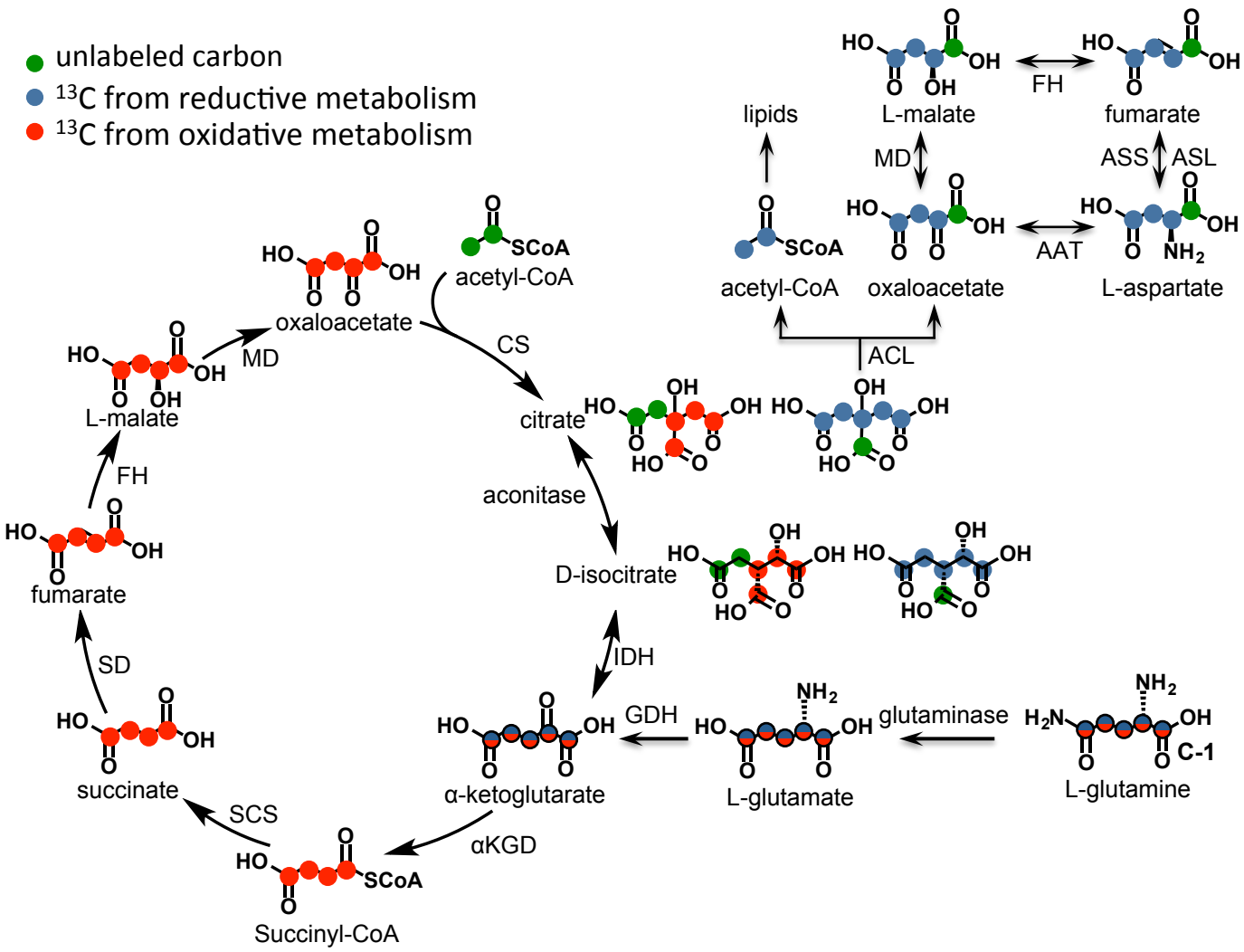
Rotenone Reduces Medium Chain Acyl-CoAs



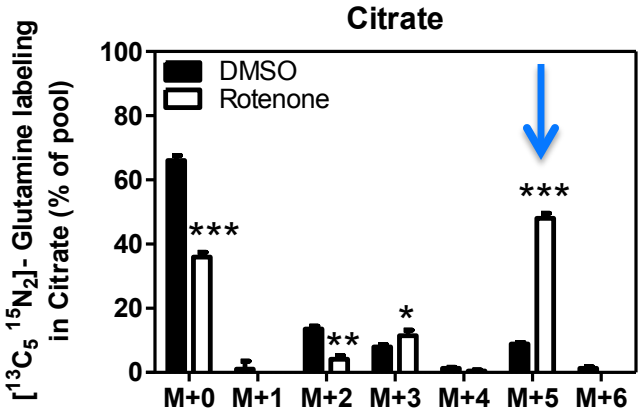
Palmitoylcarnitine Increases with Rotenone

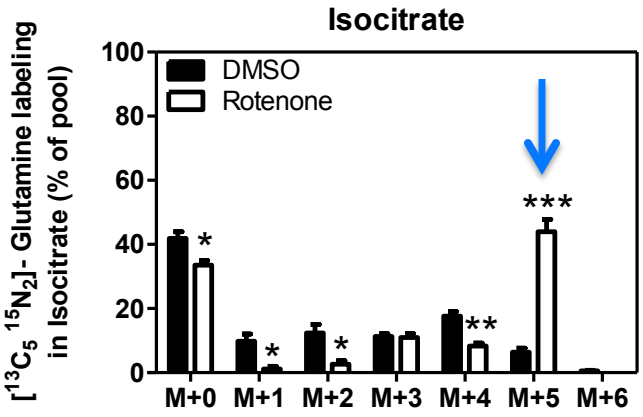


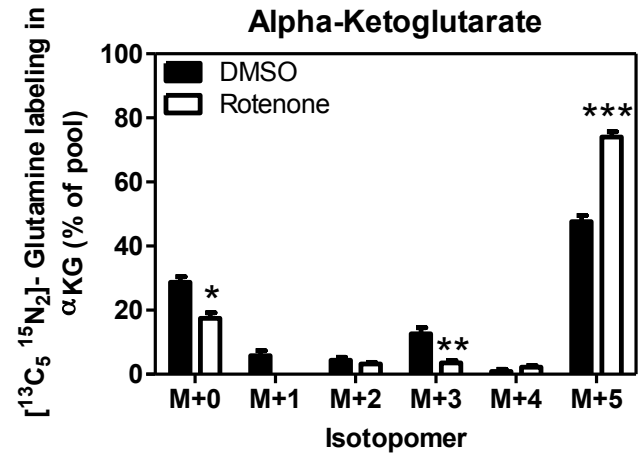
Many Roads to Acetyl-CoA

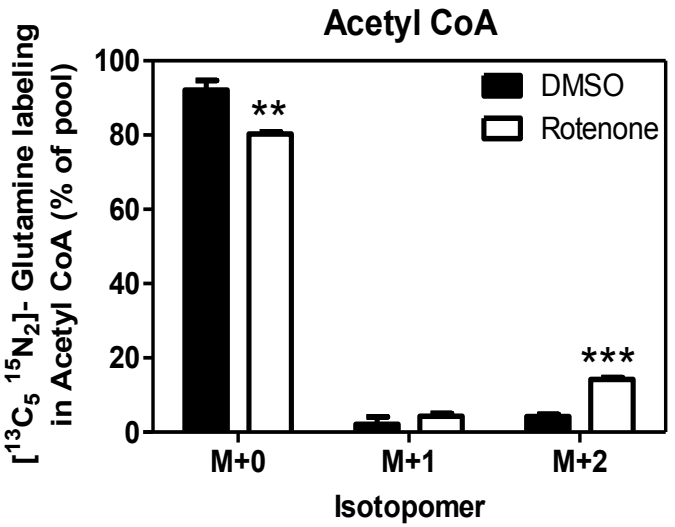


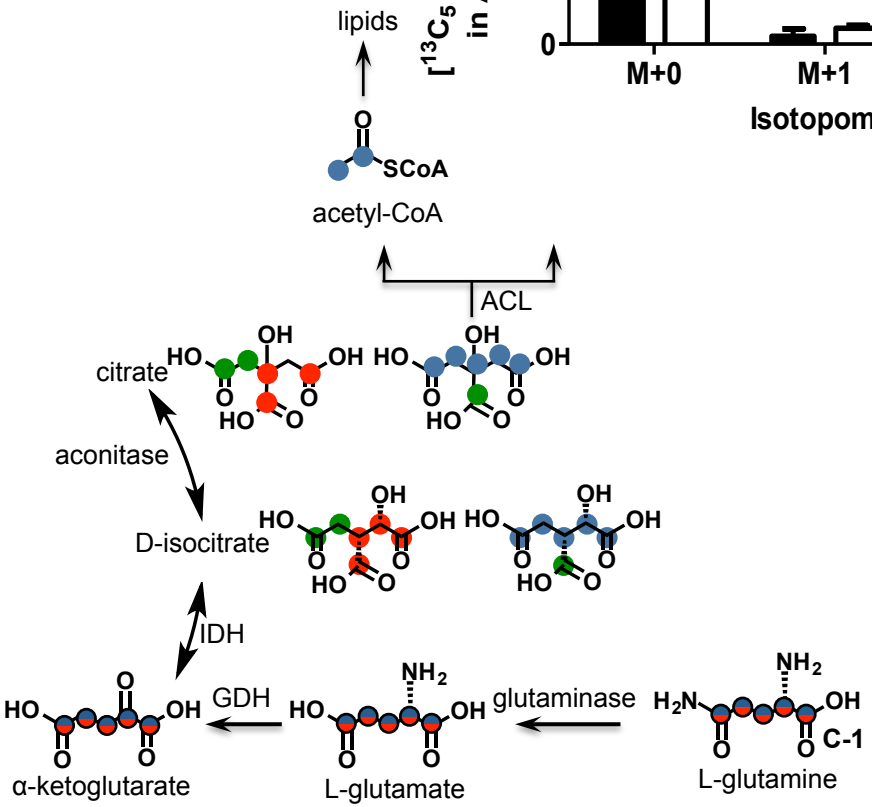
Reductive Metabolism of Glutamine



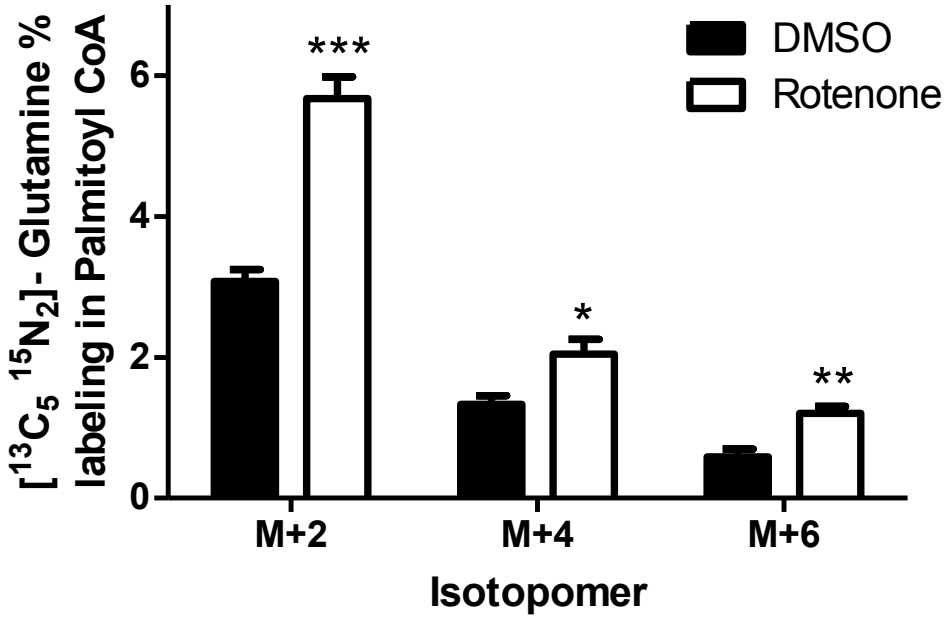






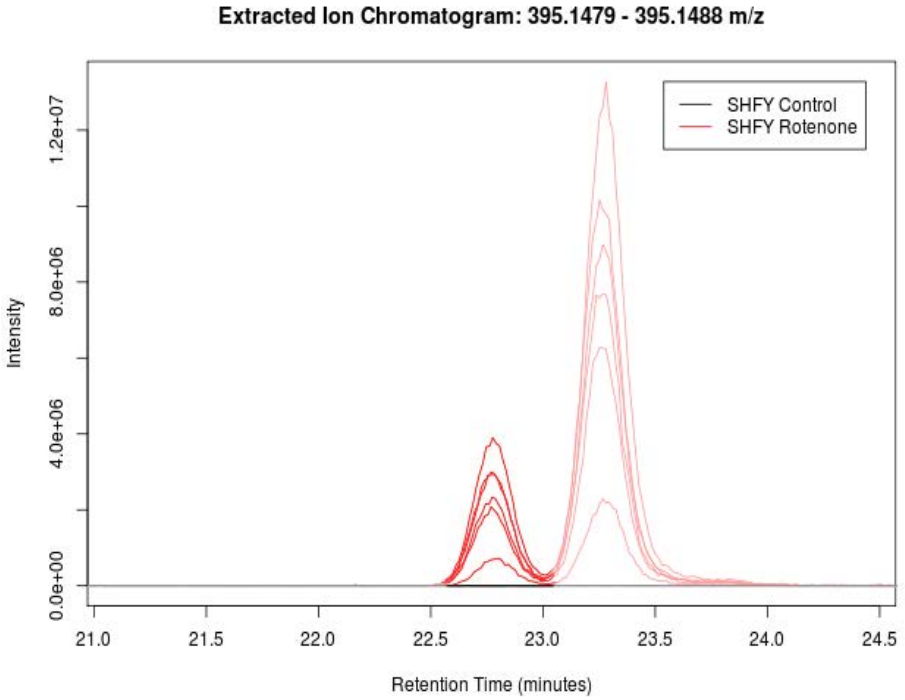


Glutamine Support Palmitoyl-CoA Synthesis

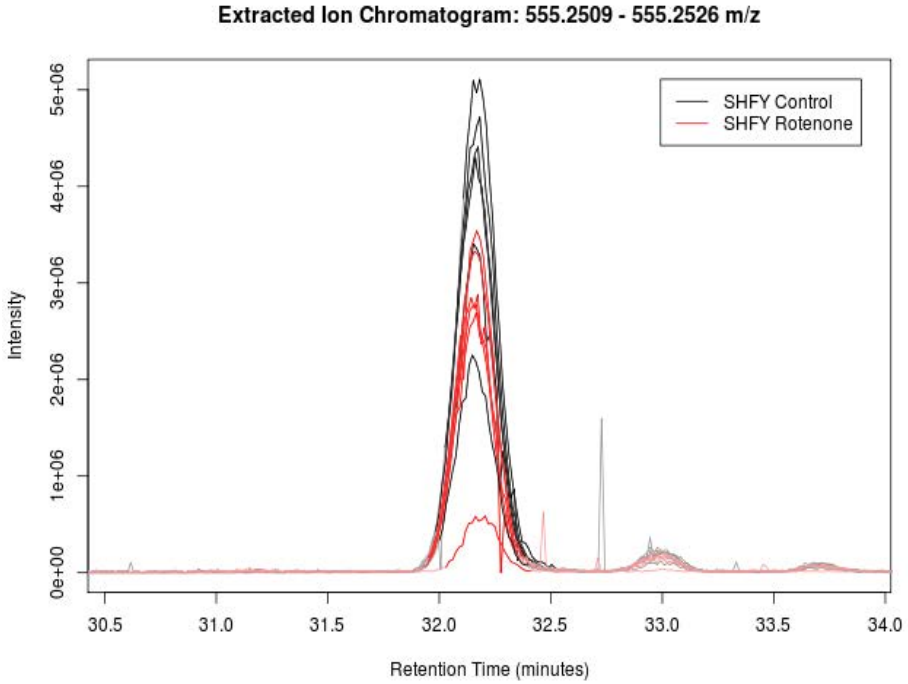


Wider Metabolic Perturbations

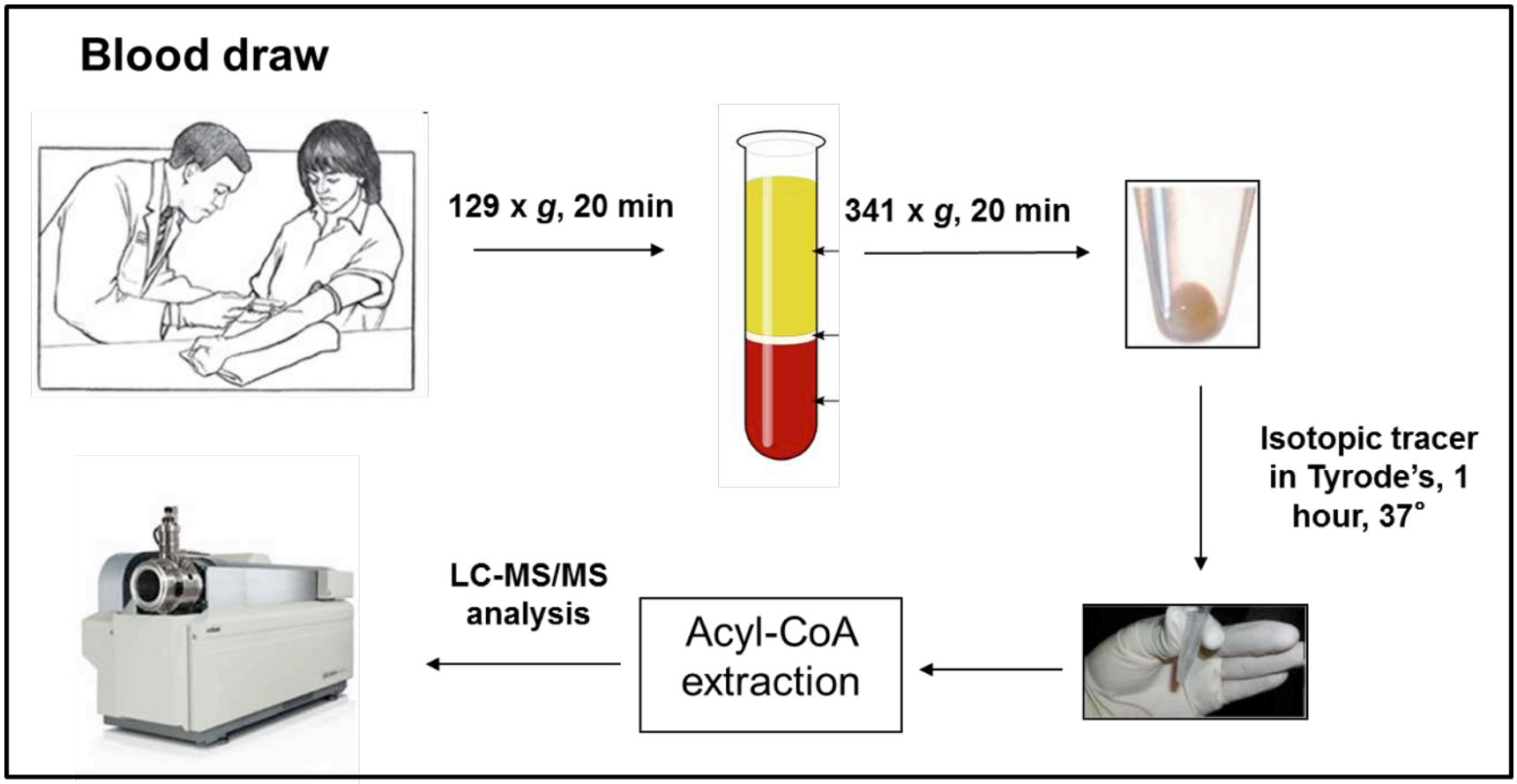
Rotenone Metabolites



D-Panthethine



Moving to New Models- Platelets

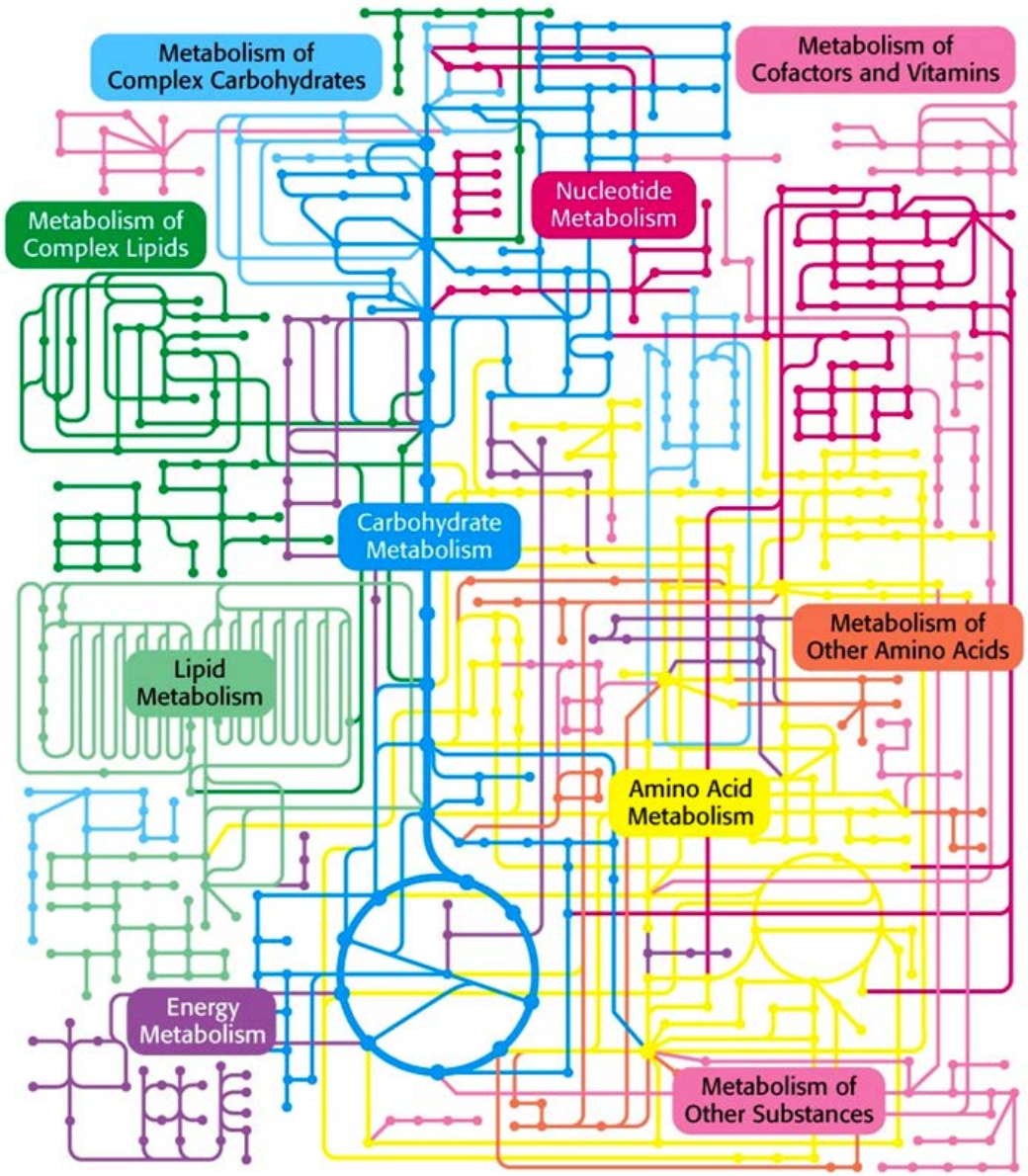


Basu, *et al*. ***Bioanalysis***. 2013. Worth, *et al*. In Preparation

Conclusions

- **Rotenone**
  - Association with Parkinson's
  - Metabolic compensation from multiple sources revealed through acyl-CoA analysis
  - Absolute quantitation has failings
  - Tracer studies to show relative contributions from different carbon sources
  - Lipid synthesis and β-oxidation?

Summary



- **Future Directions**
  - Toxicological/pharmacological mechanisms of action
  - Connect to wider metabolism
  - Better model systems for disease relevance
  - Cause or consequence?
  - Other mitochondrial complex inhibitors
  - Oxidative stress inducing exposures
  - Metabolic rescue

Acknowledgements

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