

Connecting Environmental Toxicology with Pharmaceutical Sciences through the Study of a Type 2 Diabetes Medication

Katie Edwards, Ph.D.

Department of Pharmaceutical Sciences

School of Pharmacy and Pharmaceutical Sciences

Binghamton University (SUNY)

Binghamton, NY

kedwards@binghamton.edu



Predominant theme

- Understanding impact and prevention of vitamin B1 deficiencies
- Cardiovascular symptoms
- Neurological symptoms
- Muscle weakness
- Immune system deficiencies

Not uncommon in developed countries

- *But common in developing countries*

Human diseases:

Beriberi, Wernicke-Korsakoff Syndrome

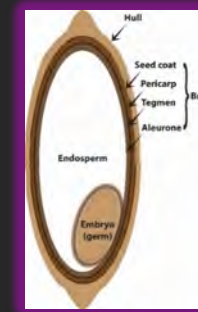
African Seasonal Ataxia, Konzo, Tropical ataxic neuropathy

Genetic defects: Roger's syndrome /TRMA, Maple Syrup urine disease

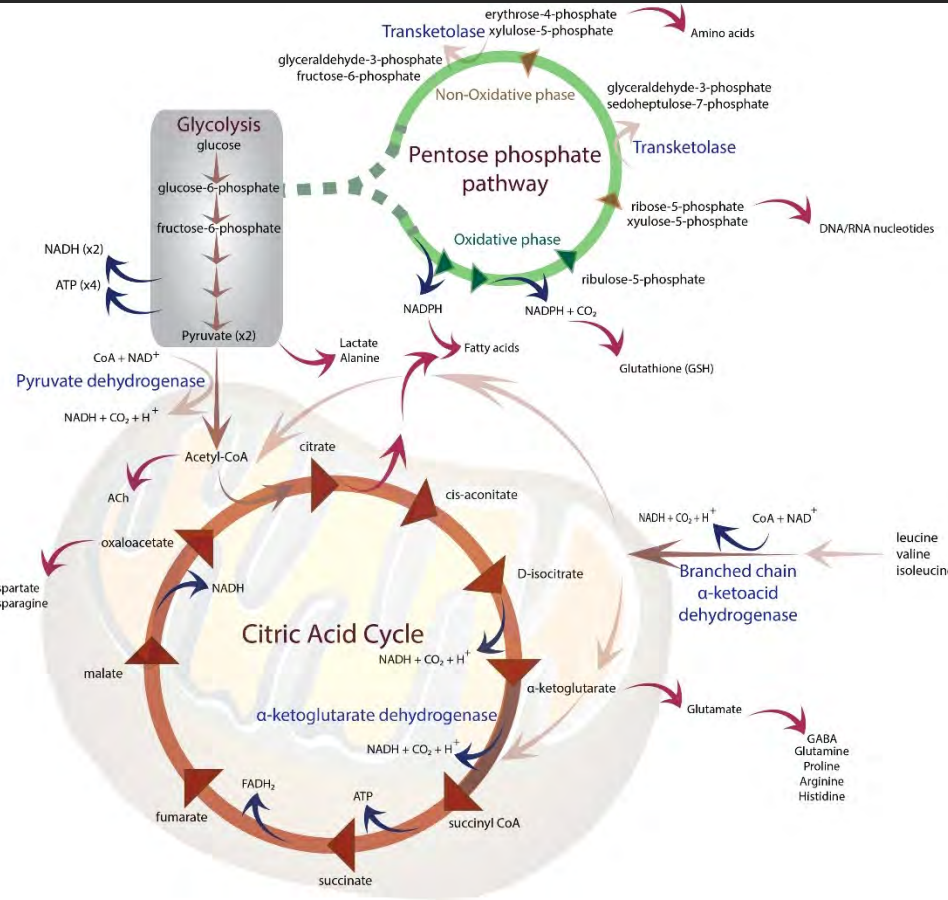
Domestic pets

Livestock: Polioencephalomalacia, Chastek's paralysis, polyneuritis

Aquatic organisms: Early Mortality Syndrome, Cayuga syndrome, M74 syndrome



www.CDC.gov



<http://thiamine.dnr.cornell.edu/>

J.M. Smucker recalls 9Lives cat food for low thiamine

Study of Israeli baby formula tragedy highlights vital vitamin B1 role

TAU research of children who had been given Remedia brand as infants and healthy peers shows thiamine crucial for nervous system

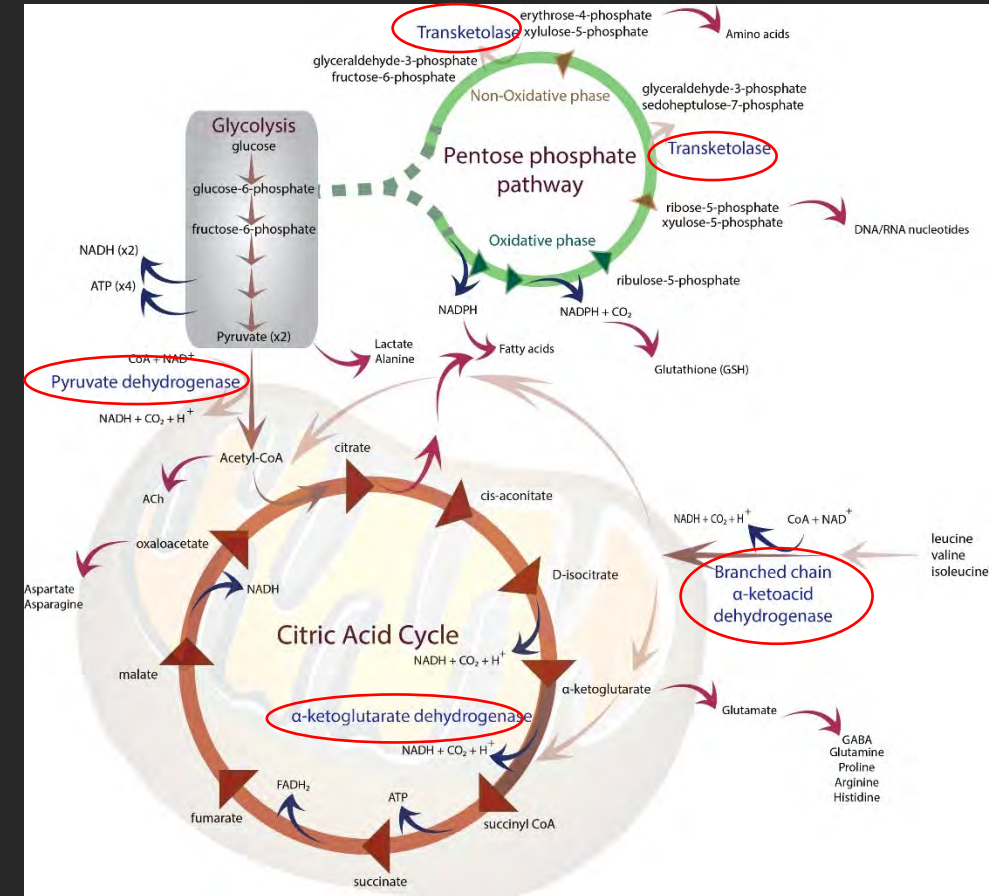
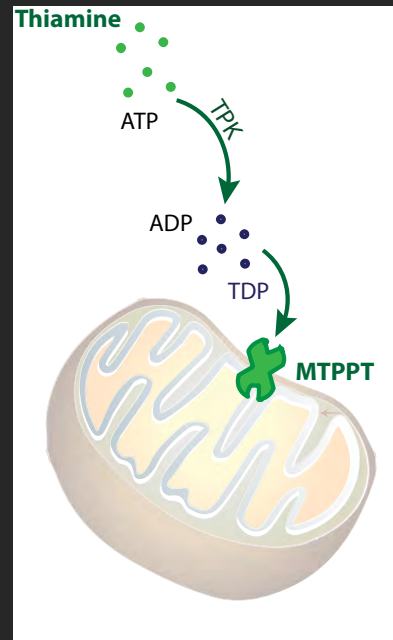
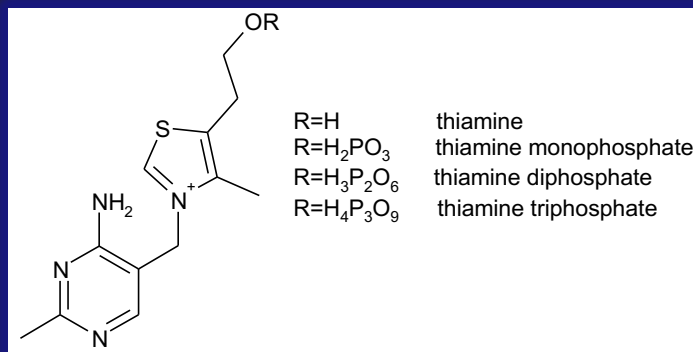
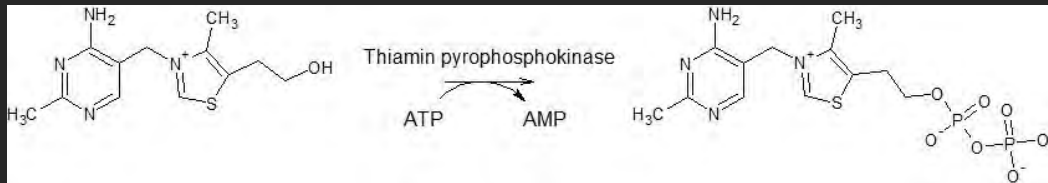


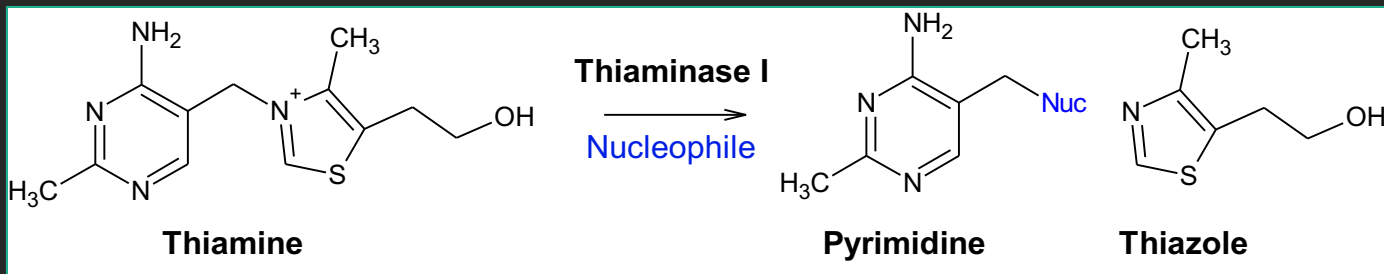
http://www2.dnr.cornell.edu/cek7/afrp_index.htm

THIAMINE BIOCHEMICAL FUNCTION

• Thiamine, in its diphosphate form, serves as a cofactor for several critical metabolic enzymes:

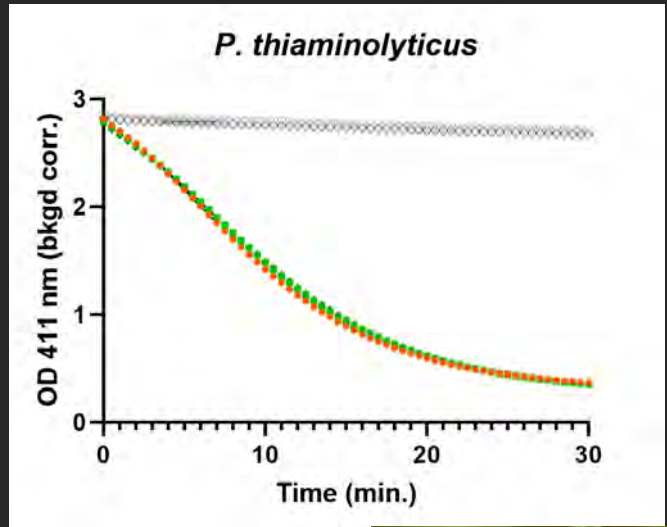
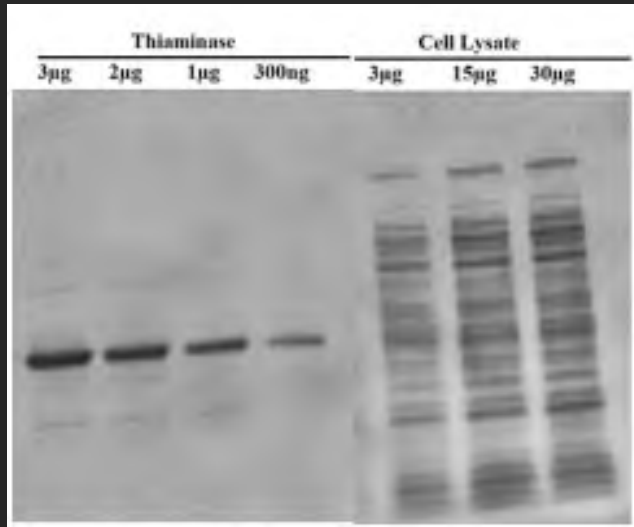
- *Pyruvate dehydrogenase (Acetyl-CoA production)*
- *α -ketoglutarate dehydrogenase (TCA cycle)*
- *Branched chain α -ketoacid dehydrogenase (metabolism of Leu, Val, Ileu)*
- *Transketolase (pentose phosphate pathway)*
- *HACL-1 (fatty acid alpha oxidation)*





Causes of B1 Deficiency

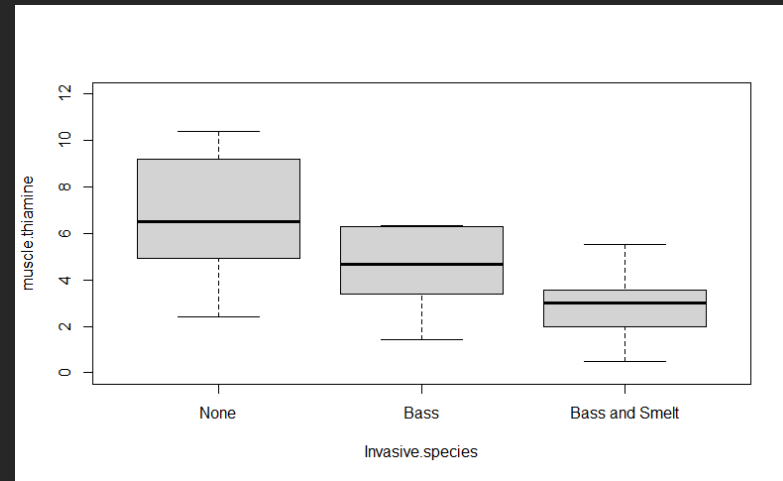
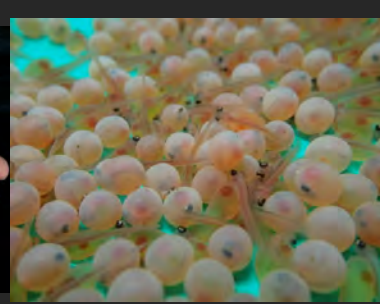
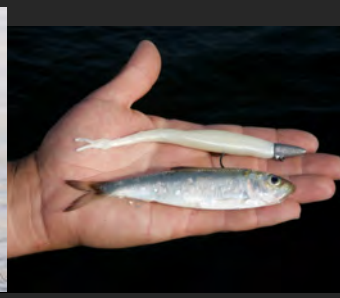
- Dietary insufficiency, complexation, or enzymatic breakdown
- Thiaminase I is produced by certain bacteria
 - Paenaebacillus thiaminolyticus*
 - Paenaebacillus apiarus*
 - Paenaebacillus dendritiformus*
 - Burkholderia thailandensis*
 - Burkholderia pseudomallei*
 - Clostridium botulinum*
 - Clostridium sporogenes*
- Some plants:
 - Bracken fern*
 - Nardoo (Marselii drumondii)*
 - Horsetail (Equisetum arvense)*
- *And some fish*



<https://www.ars.usda.gov/pacific-west-area/logan-ut/poisonous-plant-research/docs/western-bracken-fern-pteridium-aquilinum/>



Invasive Fish Species and Thiaminase



- Understanding dietary thiamine deficiency in predator fish

Hatchery diets treated with P. thiaminolyticus

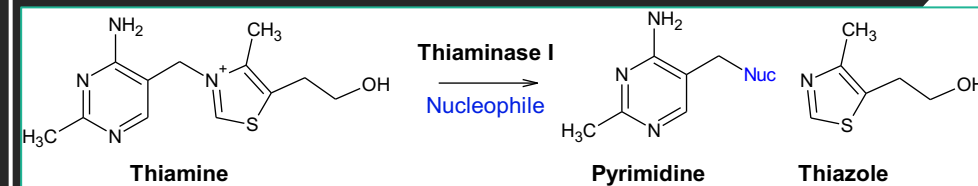
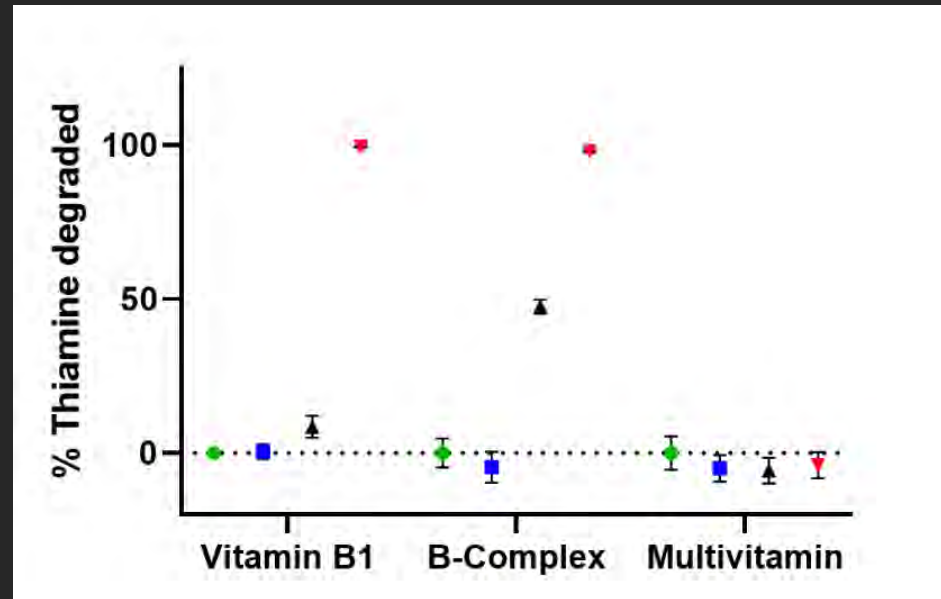
Native lake trout in inland lakes and Lake Ontario with diets of varying prey fish associated with thiaminase

Assess thiamine levels in liver and muscle tissue

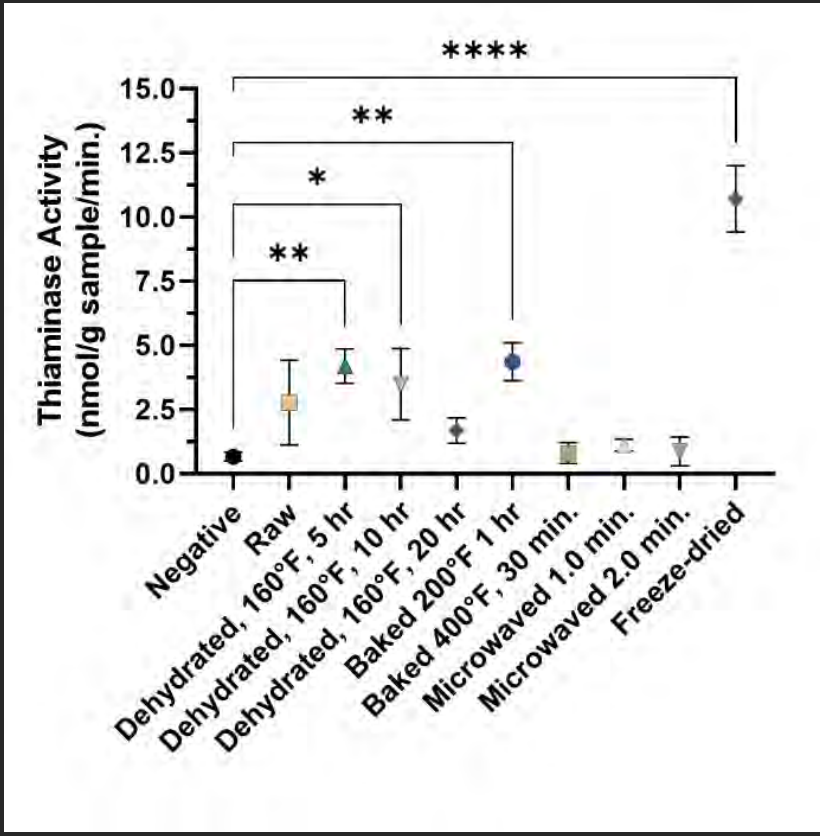
- Understanding dietary contributions to microbial thiaminase enzyme activity

Thiaminase I requires a co-substrate for thiamine degradation

What dietary constituents serve to activate and inhibit thiamine-degradating activity?

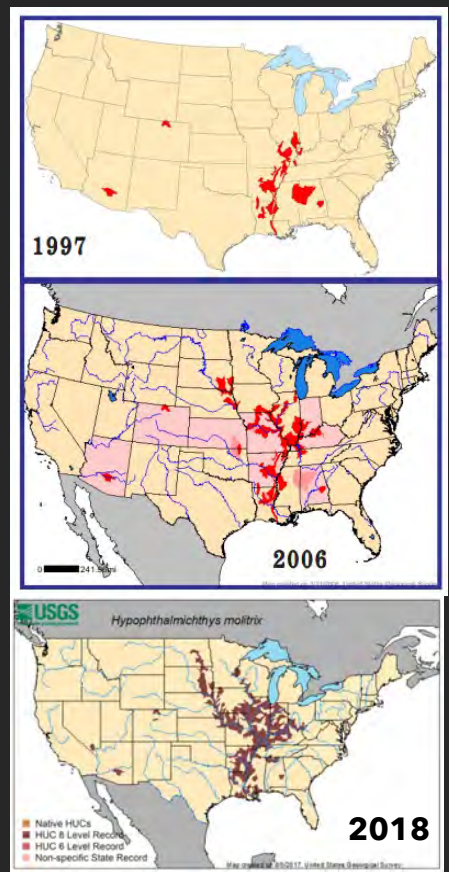


Invasive Fish Species and Thiaminase



Curr. Res. Food Sci., 6, 2023, 100502

- Understanding and inactivating thiaminase activity in Silver carp
 - Asian carp introduced to U.S. in the 1970s to control algae*
 - Escaped...*
 - Rapid proliferation throughout the U.S.*
 - Consume ~40% of their body weight/day*
 - Adults range from 20 to >80 lbs*
 - Efforts are being made to harvest them for consumption to reduce ecological impact*
 - But carp have been associated with thiaminase activity*
- How much activity and what food processing steps can effectively reduce it?
 - Baking or microwaving under certain conditions eliminated activity*
 - But, dehydration or freeze-drying under certain conditions concentrated activity without inactivation*

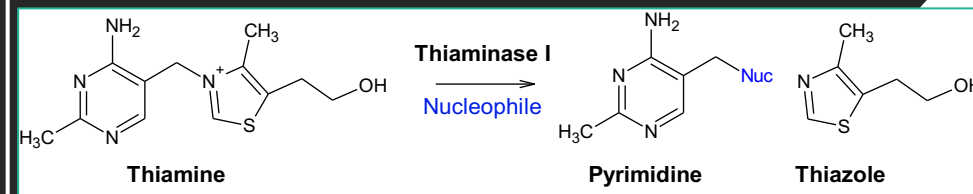


ADAPTATION

Invasive Carp of Kentucky

Episode 2 | 13m 36s |

<https://www.pbs.org/video/invasive-carp-of-kentucky-nu38pv/>



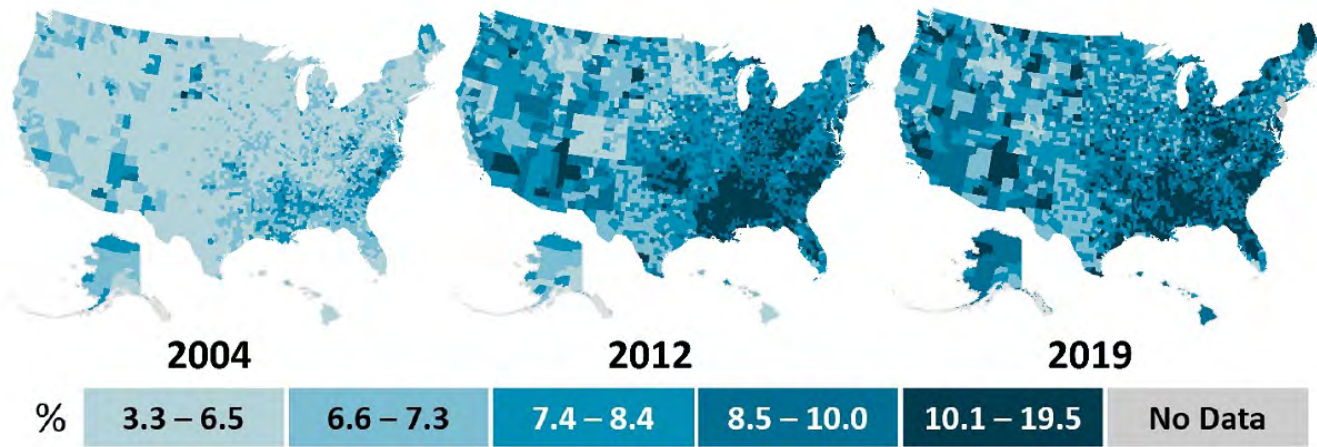


Fig. 1. Age adjusted prevalence of diabetes among U.S. adults.
Source: <http://www.cdc.gov/diabetes/data>

Metformin and Diabetes

- Most commonly prescribed drug for Type 2 Diabetes
- Prescribed to 150 million people worldwide

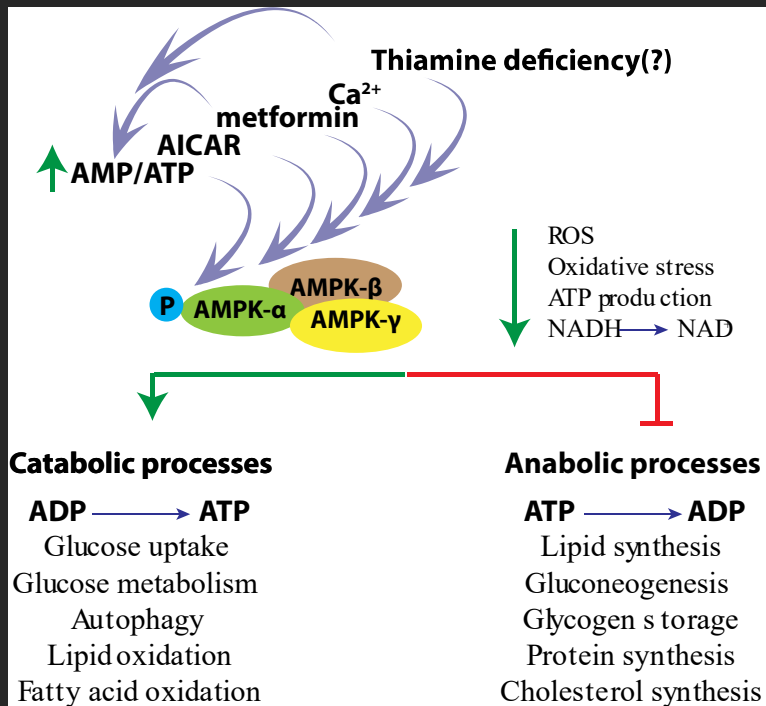
- And at high doses

Typical dosage 2x500 mg to 2x1,000 mg/day

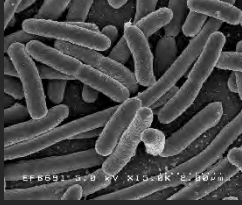
- Not metabolized

Concentrations up to 9.2 µg/L reported in Lake Michigan and up to 3.2 km off shore

Up to 27 tons of metformin are estimated to be flushed annually to the Baltic Sea and Danish strait from Sweden

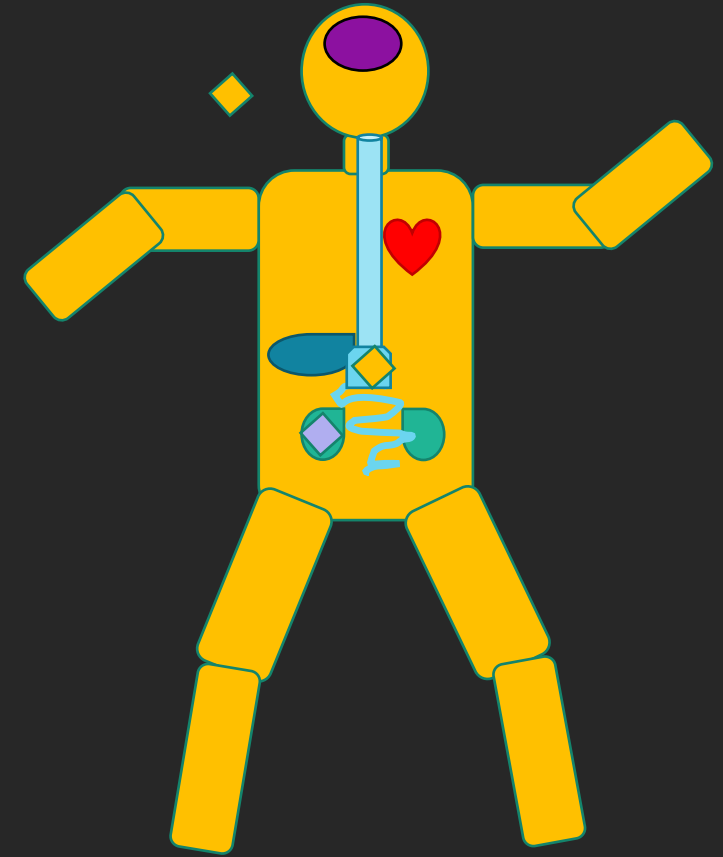
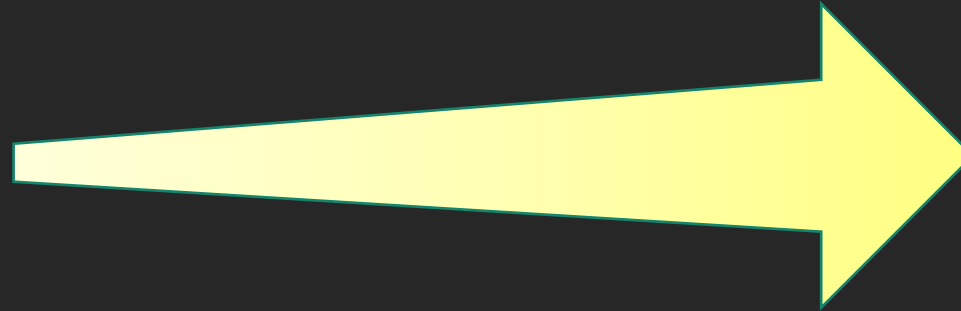


WHAT IS THE CONCENTRATION-DEPENDENT IMPACT OF METFORMIN?



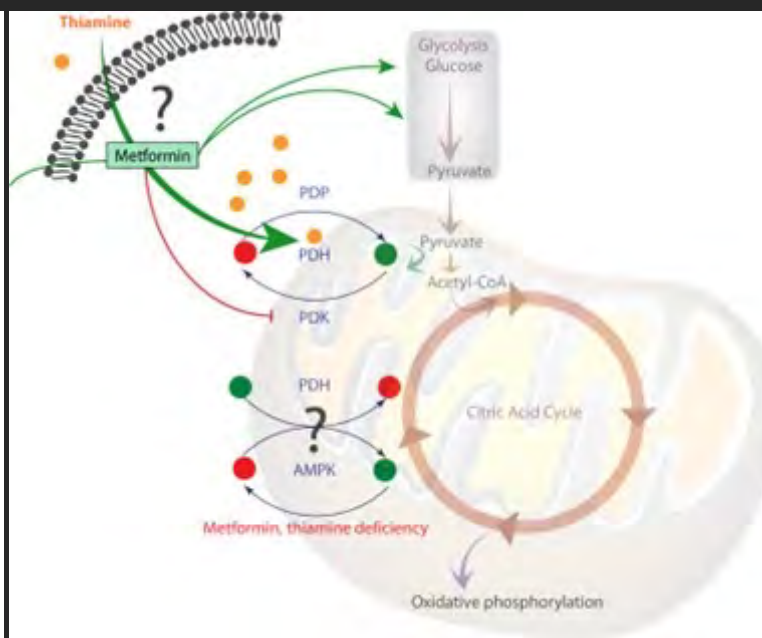
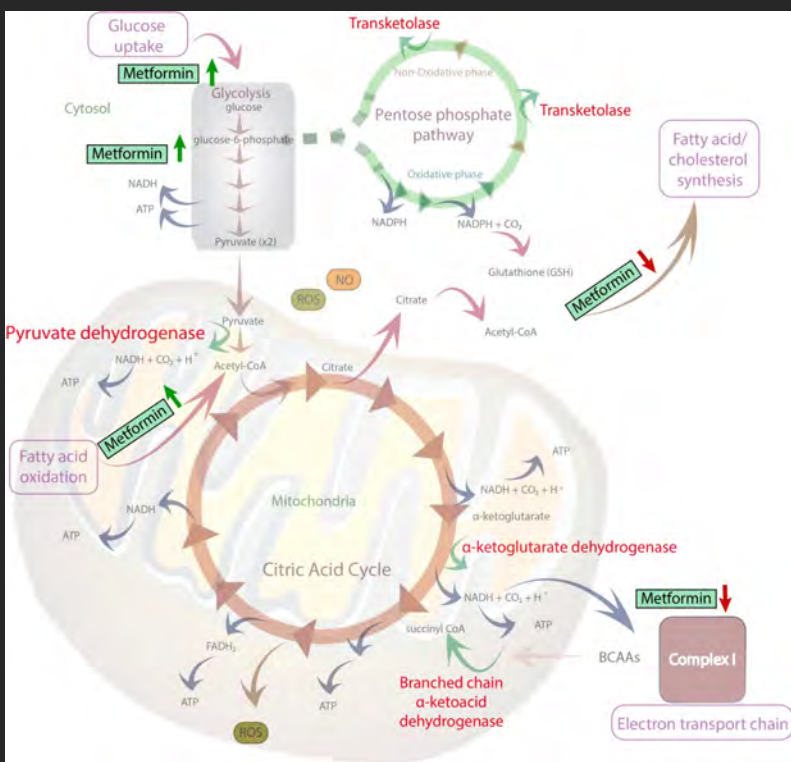
Environmental concentrations
~10 nM to 400 nM range

Endocrine disruption in *fathead minnows*
Reduced aggression in *Betta splendens*



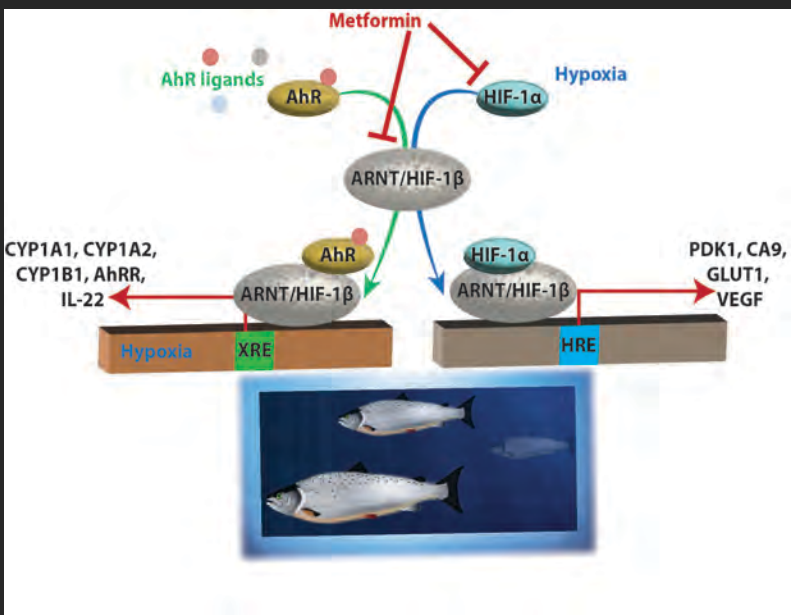
Pharmacological concentrations
 μM to mM range

AMPK activation
Complex I inhibition
Alteration of gut microbiota



Is there a linkage between metformin and thiamine deficiency?

- Thiamine impacts glucose handling
- Metformin impacts glucose handling
- Metformin shares uptake transporters with thiamine
- Metformin shares a structural backbone with thiamine
- *In humans, metformin hypothesized to compete for thiamine transporters*



Collaboration with Esther Angert, Cornell University



Collaboration with Jess Hua, University of Wisconsin-Madison

Our interests:

- How does metformin at environmental levels impact thiamine handling in bacteria, aquatic organisms, and people?
- How does metformin at environmental levels impact exposure to other stressors, such as pesticides and hypoxic environments?



Reaching Future Pharmacists

- Binghamton University School of Pharmacy and Pharmaceutical Sciences (SOPPS)

PharmD (initiated in 2017)

M.S./Ph.D. Pharmaceutical Sciences (initiated in 2022)

- Opportunity for education and outreach
Currently 21 student-led organizations
Institutional support for environmental studies
Can we improve awareness amongst the public and future pharmacists?



Acknowledgements

- Edwards lab members

Patricia Wolfe, PhD (Research Technician)

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Michaela Lynch (Undergraduate, BME)

Sophie Schwarz-Eise (Undergraduate, Biology)

Patrick Haran (Undergraduate, Biology)

- Collaborators

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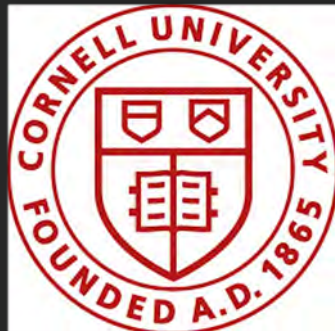
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