Possible mechanisms behind impaired glucose metabolism in niacin-deficient mice

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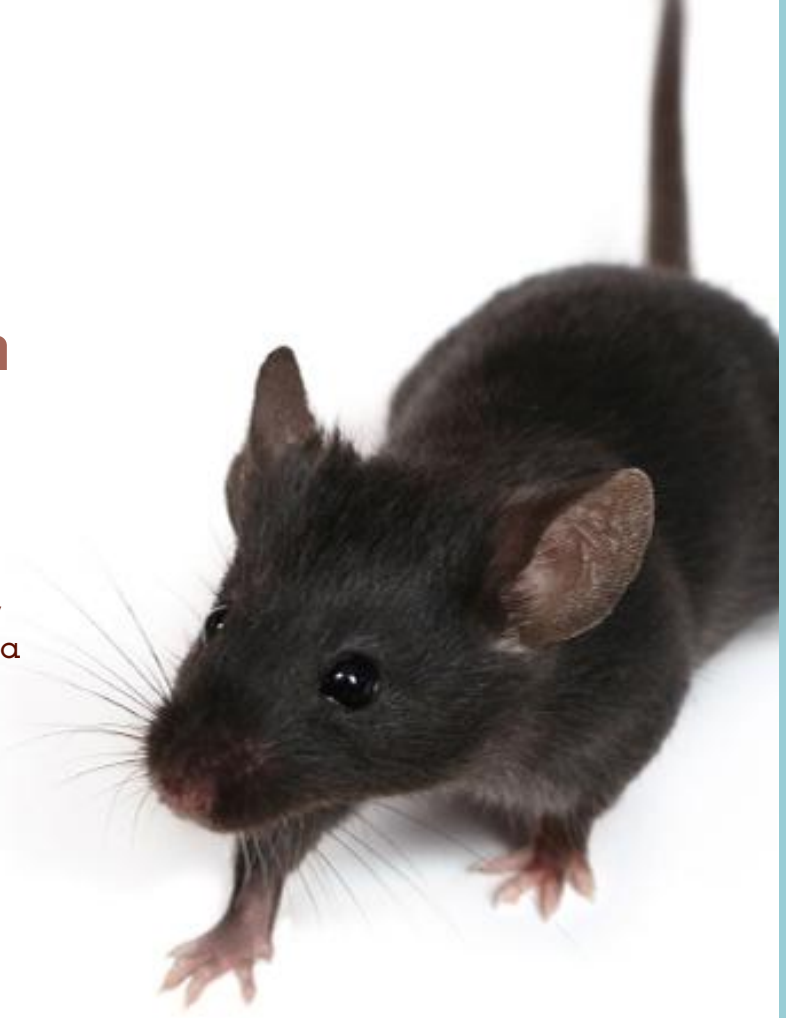
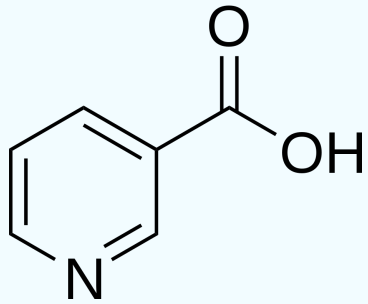


What is niacin?

- Also known as vitamin B3
- Essential for human health
- Found in animal products, some legumes (including peanuts), nuts, and vegetables
- Bread and cereals are niacin-fortified



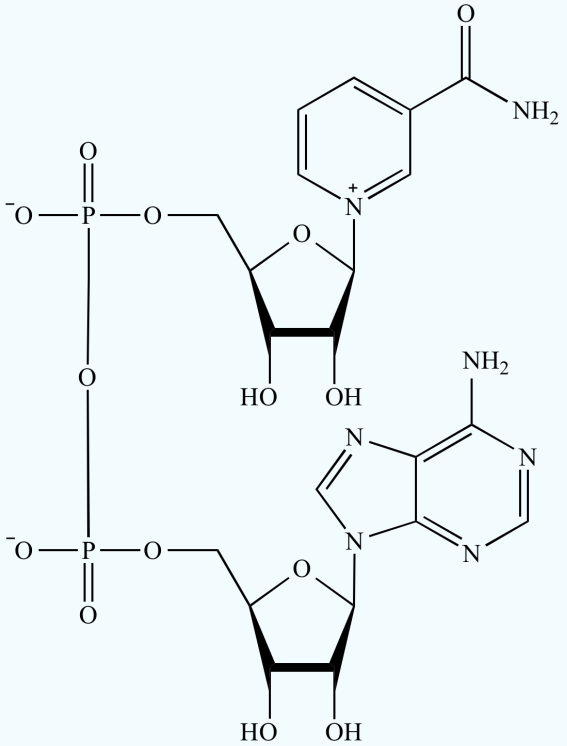
Summary:

Due to insufficient NAD+ levels during gluconeogenesis, niacin-deficient mice may be unable to properly metabolize glucose.

Niacin is important because it is synthesized to NAD+

- NAD+ = Nicotinamide adenine dinucleotide
- NAD+ is an important coenzyme

-Crucial for **skin repair, cognitive health, proper cellular function and energy metabolism**

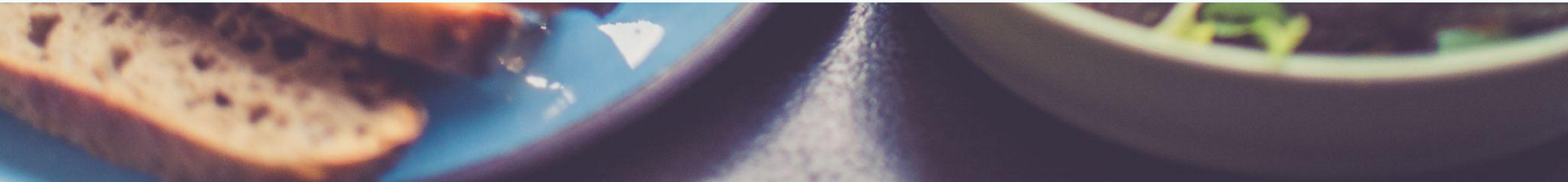


NAD+ deficiency in humans

- Severe deficiency can lead to pellagra disease= Diarrhea, dementia, dermatitis, death
- Common problem in early 1900s in poor regions in the U.S.
- Fortified food → decrease in pellagra, but health issues linked to deficiency still persist
    - -Alzheimer's and cognitive decline
    - -Impaired skin repair

NAD+ and glucose metabolism

- Metabolism= how the body processes sugars and generates ATP (energy)
- NAD+ is necessary for many metabolic pathways
    - Gluconeogénesis, the Krebs cycle, glycolysis, etc.
    - NADH (reduced NAD+) also necessary



Rationale for project

- We noticed that niacin-deficient mice had lower body weight and lower fat content than mice on normal diets
- Is there a relationship between NAD+ deficiency and glucose metabolism?
- How is this important to humans health?

  Nothing in the literature

  Vulnerable populations: the elderly, alcoholics, pregnant women, cancer patients

  Rising rates of metabolic diseases (i.e. diabetes) in U.S.

Our hypothesis:

Niacin deficiency (and therefore low NAD+ levels) negatively affect proper glucose metabolism

Study design

ANDY mouse= **A**cquired **N**iacin **D**ependency

ND

Niacin Deficient

No niacin

10 % protein

CD

Complete Diet

Adequate niacin

10 % protein

Chow

Normal Diet

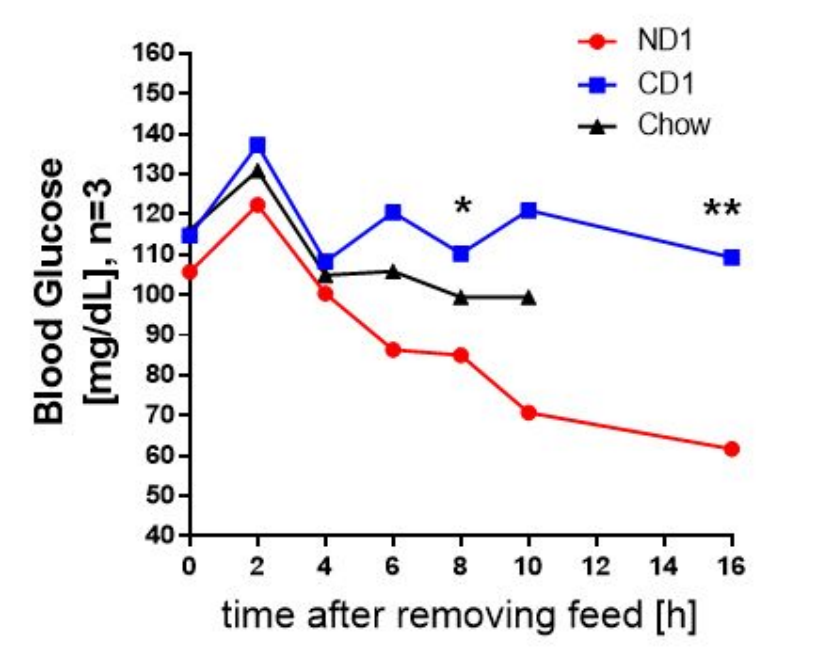
Adequate niacin

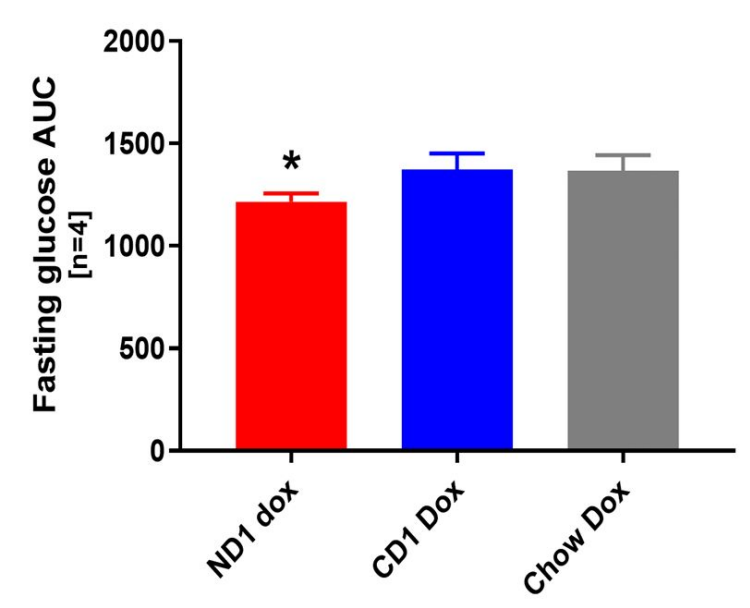
20% protein

01

Glucose Challenges

Purpose: Determine if glucose metabolism is affected by NAD+ deficiency
Method: Measure blood glucose levels while mice are fasting





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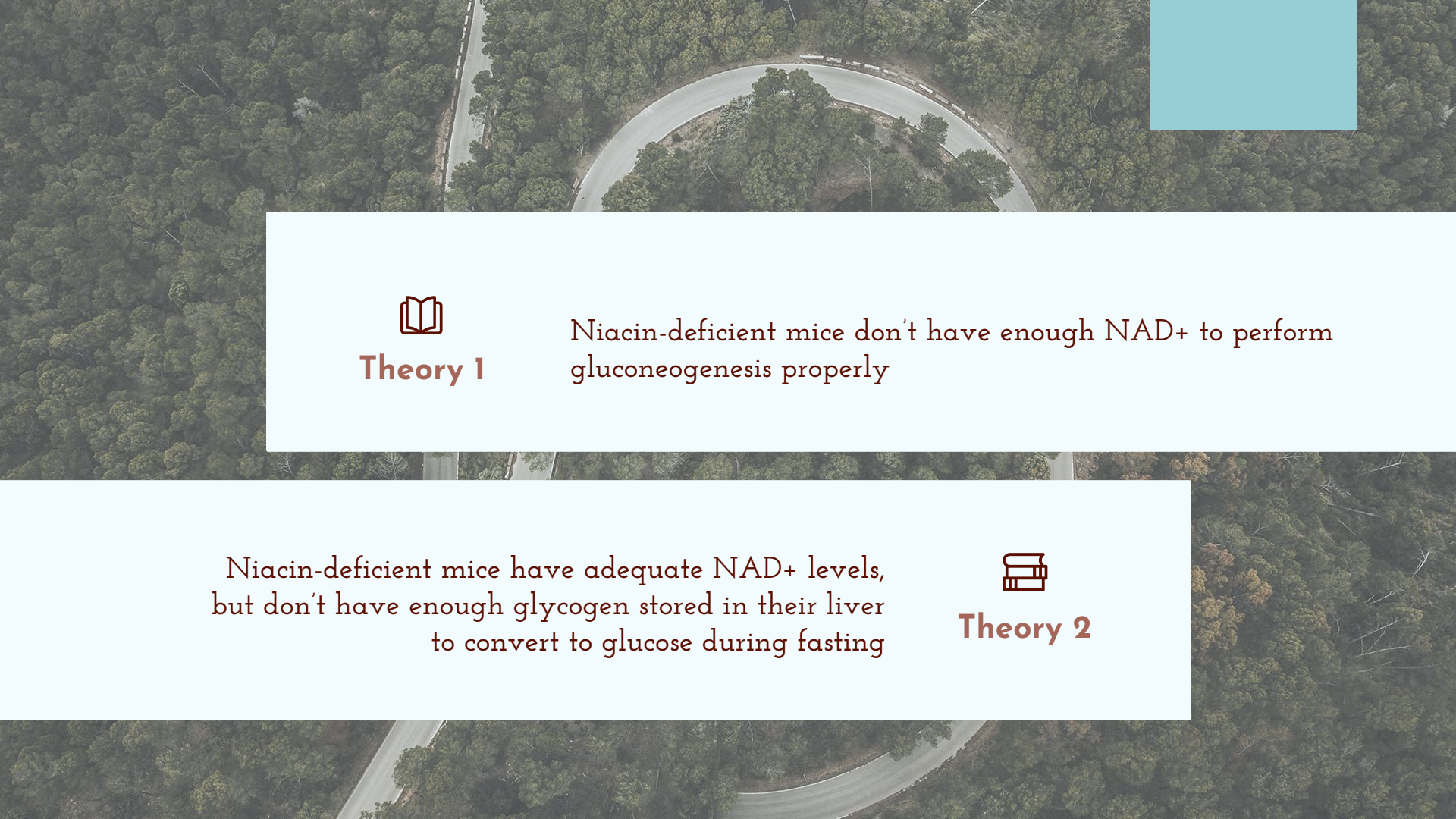
Why?



Theory 1

Niacin-deficient mice don't have enough NAD+ to perform gluconeogenesis properly

Theory 2

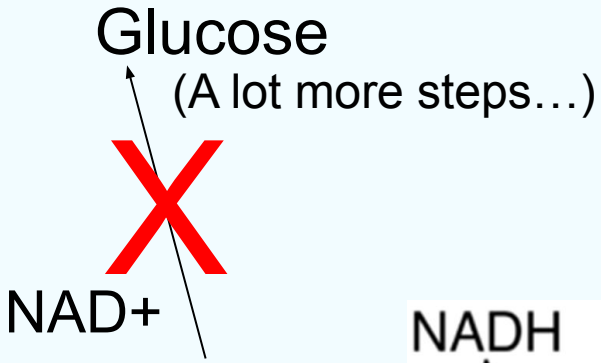
Niacin-deficient mice have adequate NAD+ levels, but don't have enough glycogen stored in their liver to convert to glucose during fasting

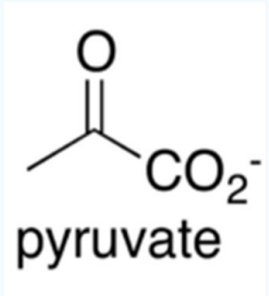
02

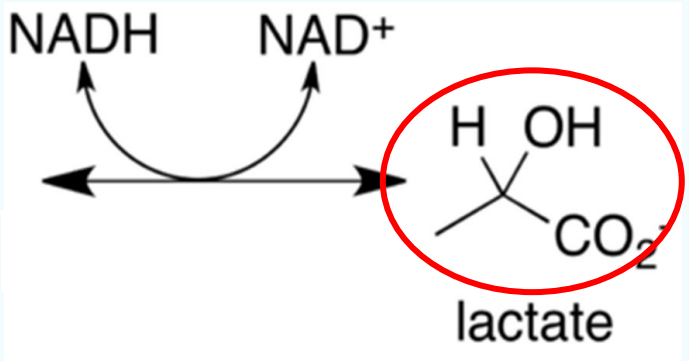
Pyruvate Challenges

Purpose: Determine if gluconeogenesis pathway is working properly
Method: Fast mice, inject with pyruvate, then measure glucose and lactate levels

- Gluconeogensis- conversion of pyruvate to glucose
- NADH: NAD+ ratio determines how/if glucose is produced
- Low NAD+ = pathway 'stuck' in lactate phase







02

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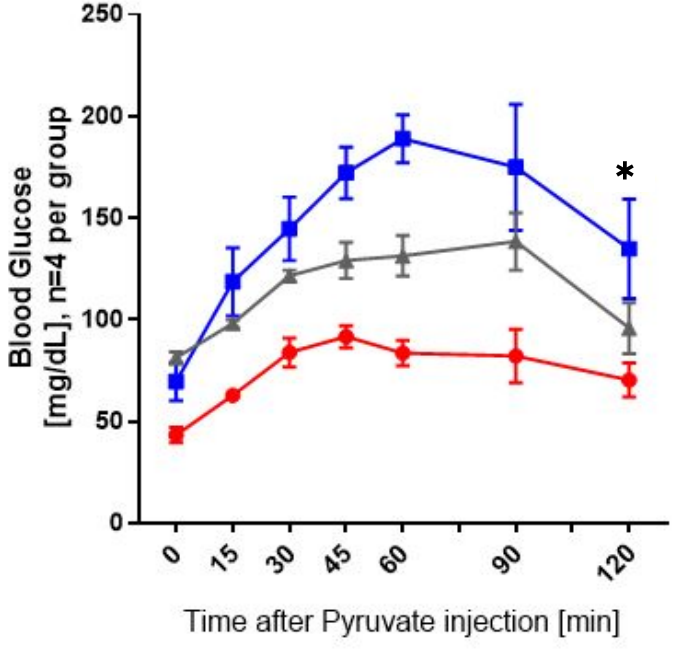
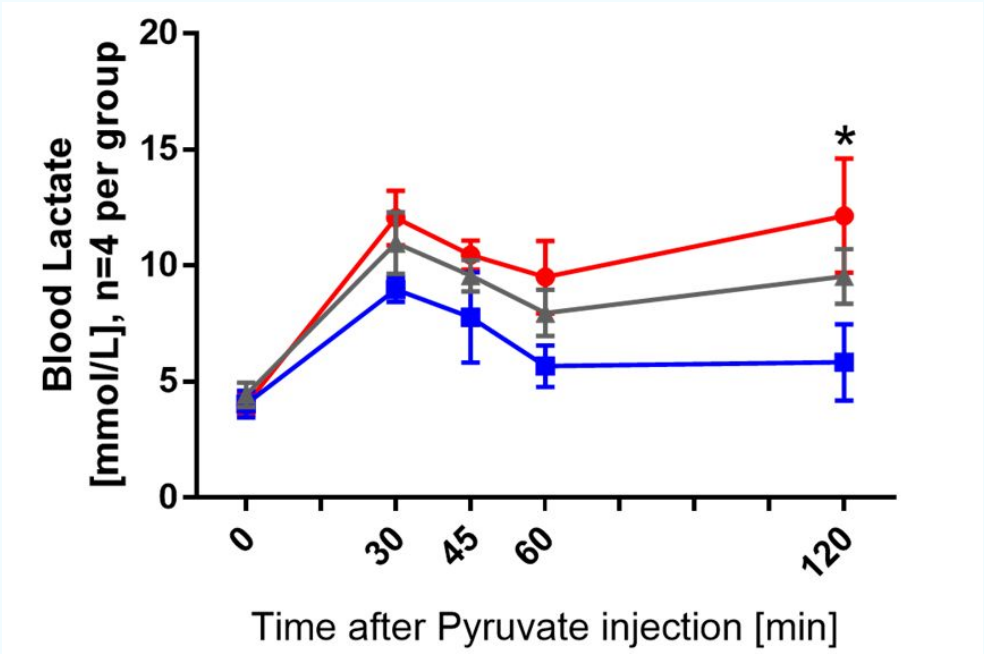




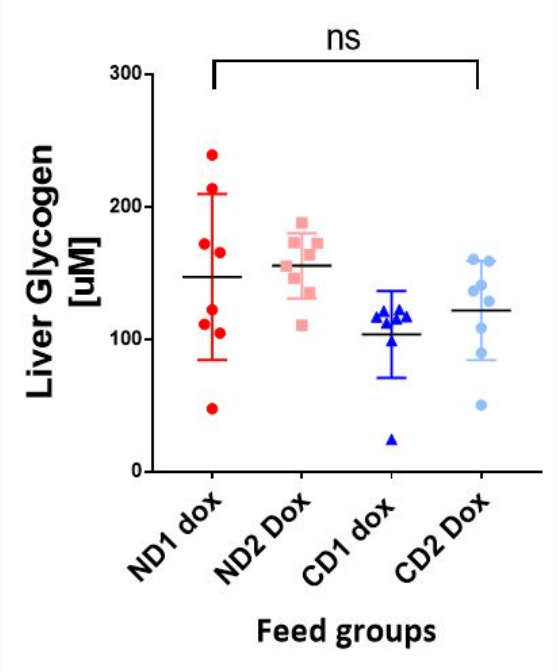
ND mice had significantly lower glucose levels (p=0.003) and higher lactate levels (p=0.0177) after pyruvate injection

03

Glycogen assays

Purpose: Determine if there is a significant difference in glycogen levels between diets
Method: Measure glycogen levels in liver post-mortem using BioVision colorimetric assay

There was no significant difference in glycogen levels between diet groups



Summary and Discussion

- Glucose metabolism is significantly different between diet groups
- There is a significant difference between diet groups when converting pyruvate to lactate during gluconeogenesis
- There is no significant different in glycogen levels between diets

- Is NAD+ levels truly the reason for imapired gluconeogenesis though?
- Possible next steps:

  Examine relationship between other important enzymes and NAD+

  qPCR analysis of enzyme expression important to metabolism

Conclusion

These findings are an important start to determining if populations that are vulnerable to niacin-deficiency are also susceptible to additional metabolic problems. If they are, how can we help them?

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Questions?