Formaldehyde Dehydrogenase-Derived Formate Contributes to Cardioprotection in the Female Heart

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Ischemic Heart Disease Is A Leading Cause Of Death

Ischemia/reperfusion (I/R) injury: inadequate blood supply reaching the heart, then more damage upon restoration of blood flow
Langendorff heart perfusion

Pre-ischemia  Ischemia  Recovery

Red tissue = alive, white = dead
Estrogen May Drive Cardioprotection

Estrogen → Unknown Processes → Cardioprotection

Formaldehyde Is Found...In The Heart?

- Estimated blood and intracellular concentrations estimated to be 87-400uM

- Background exposures can occur through food and the environment
Female Hearts Have Two-Fold More Formaldehyde Than Males

![Graph showing formaldehyde levels in males and females]

Formaldehyde (normalized ratio)

Male | Female
---|---
0.0 | 2.0

* Indicates statistically significant difference.
FDH Plays a Significant Role in Female Cardioprotection

Formaldehyde Dehydrogenase (FDH)

Cardioprotective Mechanisms

Use in one-carbon metabolism for:
• Nitric oxide signaling?
• Antioxidant defense?
FDH and ALDH2 Detoxify Formaldehyde to Formate

- Higher activity in females
- Is there a link to estrogen?


ALDH2 Activation Rescues Female FDH Knockouts

Female

ALDH2: Aldehyde Dehydrogenase 2

Infarct Size (% of Total Ventricle)

FDH
+/-  -/-  +/+  -/-

Alda-1
-  -  +  +

*  **
Does Formate Protect Against I/R Injury?

![Graph showing functional recovery and infarct size in males and females with different treatment times.](image)

- **Formate**
- **Ischemia**
- **Reperfusion with formate**

<table>
<thead>
<tr>
<th>Time</th>
<th>Formate</th>
<th>Ischemia</th>
<th>Reperfusion with formate</th>
</tr>
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<tbody>
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<td>10 min.</td>
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<td>120 min.</td>
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Recovery/Infarct Size

*Significant difference.*
Yes!

Reperfusion with formate

Recovery/Infarct Size

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Formate 25 min. 120 min.

Johns Hopkins Bloomberg School of Public Health
Formate Rescues FDH Knockout Hearts
Females Have Higher Cardiac Levels of Certain One-Carbon Enzymes

Produce formaldehyde
Formate May Serve as a One-Carbon Source in One-Carbon Metabolism

- Many cellular processes
- Link to cardioprotective signaling?
Possible Mechanism: NO Signaling

Formaldehyde $\rightarrow$ Formate

\[ \text{BH4} + \text{NOS} \]

Formate may act through the folate cycle to enhance BH4/NOS interactions

\[ \text{NO} \]

Cardioprotection
Possible Mechanism: Antioxidant Defense

• GSH:
  • Shields from reactive oxygen species (ROS)
  • Sex differences
  • Higher antioxidant capacity in females

[Chemical structures and formulas]
Formate Increases Nitrosylation in Vitro

Mechanisms to explore:
- BH4 production
- eNOS coupling
- eNOS activity other NOS isoform
Bigger Picture

• Heart disease is a leading cause of death for both men and women, but females are protected.

• Formate, a metabolite of formaldehyde, appears to protect the heart.

• Understanding the biology of the female heart may inform prevention and treatment of heart disease.
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