Presenter Disclosure Information

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Mineralocorticoid Receptors Mediate Western Diet-Induced Aortic Stiffness and Macrophage Polarization

FINANCIAL DISCLOURE:
No relevant financial relationship exists
Gender Difference on the Cardiovascular Functions Related to Obesity and Insulin Resistance

- Risk for CVD death in diabetic women is higher than in diabetic men.

- Non-diabetic premenopausal women are protected against CVD, this protection is lost in insulin resistance and T2D.

- Obesity in the setting of T2D has a more deleterious impact on diastolic dysfunction in women.

- In women, aortic stiffness, left ventricular mass and diastolic dysfunction are enhanced in states of insulin resistance and obesity.
WD Promotes Insulin Resistance in Both but Especially in Female Mice

WD–Induced Cardiac Diastolic Dysfunction in Female Mice

A

B

Role of the Mineralocorticoid Receptors in Insulin Resistance and CVD

Preliminary Data Showed Aldosterone Induces Vascular Stiffness ex vivo and in vitro

**HYPOTHESIS:**

Aortic Stiffness and Macrophage Polarization in WD fed female mice is dependent on vascular and macrophage MRs signaling.
**Animals:**
Four week-old C57BL6/J and ECMR KO female mice were fed a WD with or without 1.0mg/kg/day of chronic low dose spironolactone via subcutaneous pellet for 16 weeks.

**Groups:**
- CDC—Control diet
- CDS—Control diet with Lsp
- WDC—Western diet
- WDS—Western diet with Lsp
Low Spirolactone Inhibits WD–Induced Aortic Stiffness Without Blood Pressure Changes in vivo

Catheter blood pressure under surgical anesthesia in vivo
Low Spirolactone Inhibits WD–Induced VSMC and EC Stiffness ex vivo
Low Spirolactone Prevents WD– Impaired Aortic Dilation Function ex vivo
MR Mediates WD–Induced Aorta Macrophage M1/M2 Polarization

**A**

- **M1 markers**
  - MCP 1
  - CD 86
  - CD 11b

- **M2 markers**
  - IL 10

* Fold change in mRNA levels

**B**

- **Ratio of M2/M1 mRNA**
  - IL10/MCP1
  - IL10/CD86
  - IL10/CD11b

* Significant differences

Legend:
- CDC
- CDS
- WDC
- WDS

Error bars represent standard deviation.
Low Spirolactone Restores WD– Obligate Impairment of Insulin Metabolic Akt/eNOS Signaling Pathways
CAN MR OF THE ENDOTHELIAL CELLS BE INDEPENDENTLY INVOLVED IN THE VASCULAR AND CARDIAC STIFFNESS IN FEMALE MICE?
EC-specific MR KO mouse

Mice from Dr. Iris Jaffe in Tufts University
ECMR KO Prevents WD–Induced Aortic Stiffness and Cardiac Diastolic Dysfunction in vivo

**Aortic PWV (m/s)**

- CDC: 6
- CDKO: 6
- WDC: 8
- WDKO: 10

**P-values**:
- P<0.001
- P<0.02

**Tissue Doppler E'/A'**

- CDC: 1.8
- CDKO: 1.5
- WDC: 1.3
- WDKO: 1.2

**Isovolumic Relaxation Time (ms)**

- CDC: 15
- CDKO: 17
- WDC: 28
- WDKO: 20

*† denotes statistical significance.
ECMR KO Prevented WD- induced Aortic Dilation Dysfunction ex vivo

- **Percent maximal dilation**
  - Ach (-log M)
  - Sodium nitroprusside (-log M)
  - Insulin (ng/ml)

- **Graphs** show the percent maximal dilation for different conditions:
  - CDWT
  - CDKO
  - WDWT
  - WDKO

- **Significance** indicated by asterisks (*)
Our previous studies support that mineralocorticoid receptors mediate WD--induced insulin resistance and cardiac diastolic dysfunction in female mice.

Mineralocorticoid receptors mediate WD--induced aortic stiffness and dilation dysfunction through impairment of insulin metabolic AKT/eNOS signaling pathways in female mice.

Mineralocorticoid receptors mediate WD--promoted macrophage M1/M2 polarization in aorta in female mice.

Both EC MR KO and low spirolactone can prevent WD--induced cardiac and aortic stiffness in female mice.
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