Leptin-Mediated Aldosterone Secretion Causes Hypertension in Obese females

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Presenter Disclosure Information

• Eric J. BELIN de CHANTEMELE, Ph.D
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FINANCIAL DISCLOSURE:
No relevant financial relationship exists
Obesity Affects more Women than Men

National Health and Nutrition Examination Survey 2011-12

CDC, NCHS Data Brief #131 October 2013
Obesity is a Main Risk Factor for Hypertension


Does obesity lead to hypertension via similar mechanisms in males and females?

Leptin contributes to Obesity-Related Hypertension in Males

- The adipokine leptin highly contributes to hypertension in males by increasing sympathetic activity
Females?


- Obese patients exhibit inappropriately high aldosterone levels. (Calhoun DA, *Cardiol Clin.* 2010)

- Plasma aldosterone levels are correlated with the degree of adiposity and blood pressure in women only. (Goodfriend TI, *Obes. Res.* 1999, El-Gharbawy et al. *Hypertension* 2001)

Hypothesis

Leptin Induces Hypertension via Aldosterone-Dependent Mechanisms in Obese Females.
Mouse Models

**Leptin Sensitization**

**Ptp1b KO mice**

La Cava A, *Nature Reviews Immunology* 2004
Mouse Models

Leptin Sensitization
Ptp1b KO mice

Obesity
Agouti Yellow Obese Mice

WT     KO

a/a     Ay
Leptin-sensitization and Obesity Leads to Hypertension in Female mice

Ptp1b KO Mice

Agouti Yellow Obese Mice

*p<0.05 vs. WT

*p<0.05 vs. a/a
Leptin Receptor Antagonism Restores Blood Pressure

* $p < 0.05$ vs. WT, $^* p < 0.05$ vs. KO

* $p < 0.05$ vs. WT, $^* p < 0.05$ vs. a/a, $^# p < 0.05$ vs. Ay
Leptin Sensitization and Obesity Do not Increase Sympathetic Tone in Females

Ptp1b KO Mice

Agouti Yellow Obese Mice

* p<0.05 vs. WT

* p<0.05 vs. a/a
Leptin Sensitization and Obesity Do not Increase Plasma Catecholamine Levels

Ptp1b KO Mice

- Norepinephrine (pg/ml)
  - WT: ~2000
  - KO: ~1500

- Epinephrine (pg/ml)
  - WT: ~3000
  - KO: ~1000

Agouti Yellow Obese Mice

- Norepinephrine (pg/ml)
  - a/a: ~1500
  - Ay: ~2000

- Epinephrine (pg/ml)
  - a/a: ~1500
  - Ay: ~2500

*p<0.05 vs. WT

*p<0.05 vs. a/a
Leptin Sensitization and Obesity Increase Aldosterone Signaling

Ptp1b KO Mice

Agouti Yellow Obese Mice

*p<0.05 vs. WT
*p<0.05 vs. a/a
Leptin Receptor Blockade Reduces Blood Pressure in Female mice only

Ptp1b KO Mice

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>KO</th>
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</thead>
<tbody>
<tr>
<td>Aldosterone (pg/ml)</td>
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</table>

Agouti Yellow Obese Mice

<table>
<thead>
<tr>
<th></th>
<th>a/a</th>
<th>Ay</th>
<th>a/a+ Allo-aca</th>
<th>Ay+ Allo-aca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone (pg/ml)</td>
<td></td>
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*Cp<0.05 vs. WT, #p<0.05 vs. KO

CYP11B2

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<tr>
<th></th>
<th>WT</th>
<th>KO</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP11B2/actin</td>
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<td></td>
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</tbody>
</table>

*Cp<0.05 vs. WT, #p<0.05 vs. KO

* p<0.05 vs. a/a, # p<0.05 vs. Ay
Mineralocorticoid Receptor Inhibition Reduces Blood Pressure in Female mice only

**Ptp1b KO Mice**

- WT
- KO
- WT+ spiro
- KO+ spiro

**Agouti Yellow Obese Mice**

- a/a
- Ay
- a/a+ spiro
- Ay+ spiro

* $p<0.05$ vs. WT, # $p<0.05$ vs. KO

* $p<0.05$ vs. a/a, # $p<0.05$ vs. Ay
Question

How does leptin regulate aldosterone signaling?
Human Adrenocortical Cells Express Leptin Receptor
Leptin Increases Aldosterone Signaling In Human Adrenocortical Cells

*\( p<0.05 \) vs. vehicle, \( \# p<0.05 \) vs. lep10, \( \$ p<0.05 \) vs. lep50
Leptin Increases Aldosterone Signaling *In Vivo*

* *p<0.05 vs. vehicle*
Leptin Increases Aldosterone Signaling *In Vivo* Independently of RAAS and ANS

*p* < 0.05 vs. vehicle
Deficiency in Leptin Receptor Blunts Obesity-induced Increase in Aldosterone Signaling

*\( p<0.05 \) vs. CD
Conclusion

• Leptin induces hypertension via aldosterone-dependent mechanisms in females

• Obesity-related hypertension is leptin dependent and involves aldosterone in females

• Leptin is a direct regulator of aldosterone secretion

• Leptin and obesity-mediated cardiovascular dysfunctions are sex-specific.
With the present study we are providing evidence to support:

- The development of personalized medicine and notably the development of sex-based therapy
- The use of Mineralocorticoid Receptor antagonist for treatment of hypertension in obese women
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American Heart Association
Learn and Live
Females Secrete 4 Times more Leptin than Males

Haupt DW et al., Neuropsychopharmacology (2005) 30, 184–191
Analysis of the Interaction Between Leptin and Aldosterone in Humans

- Population
  - Young healthy normotensive adults: Age 20-40
  - 8 men, 13 women
  - Non-smokers
  - No treatment
  - Women were both naturally cycling and oral contraceptive users. All tested in the early follicular phase or during the placebo period.
Aldosterone Correlates Positively to Leptin in Women Only

- Women: $R^2 = 0.34348$
- Men: $R^2 = 0.052$

- Women: $R^2 = 0.63902$
- Men: $R^2 = 0.1017$
Leptin Increases Aldosterone Signaling *In Vivo*

Huby, Gomez-Sanchez, Belin de Chantemele, Circulation in Press
Leptin Elevates Blood Pressure via Aldosterone-Dependent Mechanisms in Females

- Leptin sensitization and obesity elevate blood pressure and increase aldosterone signaling
- Leptin receptor antagonism decreases aldosterone signaling and restores blood pressure
- Inhibition of aldosterone action via MR blockade restores blood pressure
Women Develop More Severe Forms of Obesity than Men

Women had significantly higher obesity rates compared to men.

CDC, NCHS Data Brief #56 March 2011

Notes:
1 Significantly different from estimate for Canada (p < 0.05).
2 Use with caution (coefficient of variation 16.6–33.3%).
The Leptin Hypothesis

Aldosterone

Adrenal Glands

Leptin

Adipose tissue

Vascular Dysfunction
Cardiac Impairment
Sodium Retention

HYPERTENSION
The Leptin Hypothesis

Adrenal Glands

Aldosterone

Leptin

Adipose tissue

Hypothalamus

Sympathetic activity

Vascular reactivity

Heart Rate

Sodium Excretion

Vascular Dysfunction
Cardiac Impairment
Sodium Retention

HYPERTENSION

HYPERTENSION
Background (1)

- The epidemic of obesity induced a 3 fold increase in the occurrence of cardiovascular events in women of reproductive age. (Towfighi A, Neurology 2007, Arch Intern Med 2009, Cerebrovasc Dis 2011)

- Obese patients exhibit inappropriately high aldosterone levels. (Calhoun DA, Cardiol Clin. 2010)


- Plasma aldosterone levels are correlated with the degree of adiposity and blood pressure in women only. (Goodfriend TI, Obes. Res. 1999, El-Ghabawy et al. Hypertension 2001)

Conclusion

Leptin

Adrenal Glands

Aldosterone

Vascular Dysfunction
Cardiac Impairment
Sodium Retention

Hypertension

Cardiac Impairment
Sodium Retention

Adipose tissue

Leptin

Hypothalamus

Sympathetic activity
Vascular reactivity
Heart Rate
Sodium Excretion

Hypertension
Figure 3. Supine and standing PRA and plasma aldosterone in subjects with the metabolic syndrome and in subjects without the metabolic syndrome.

C de Haro Moraes et al., *Journal of Human Hypertension* (2013) **27**, 225–230
Obesity affects more women than men.
Aldosterone contributes to hypertension independently of the RAS

The Leptin Hypothesis

Adipose tissue → Leptin → Hypothalamus

- Appetite
- Food intake
- Sympathetic activity
  - Energy expenditure

→ Body weight
The Leptin Hypothesis

Adipose tissue → Leptin → Hypothalamus

Hypothalamus → Sympathetic activity

Sympathetic activity → Heart Rate 

Heart Rate → Vascular reactivity 

Vascular reactivity → Sodium Excretion 

Sodium Excretion → HYPERTENSION
The Leptin Hypothesis

Leptin from adipose tissue affects the hypothalamus, leading to sympathetic activity, which in turn affects vascular reactivity, heart rate, and sodium excretion, resulting in hypertension.