Cardiovascular Biology of the Leptin/Melanocortin System

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Disclosure of Relationships
Over the past 12 months

No relationships to disclose
Obesity is a major cause of human essential hypertension.
Weight gain is positively associated with increases in arterial pressure.


Mechanisms of Obesity-Induced Hypertension

- Intrarenal abnormalities (including physical compression of the kidneys by surrounding visceral fat)
- Activation of the renin-angiotensin-aldosterone-system
- Sympathetic nervous system activation
Chronic adrenergic receptor blockade and bilateral renal denervation markedly blunt obesity-induced hypertension


\(\alpha + \beta\) adrenergic blockade decreases ambulatory mean arterial pressure more in obese than in lean hypertensive patients

Potential mechanisms leading to increased sympathetic activation in obesity
Chronic leptin infusion, at rates that mimic leptin levels in severe obesity, raises BP and HR in lean rats

Shek EW et al. Hypertension 31:409-14, 1998
Chronic $\alpha + \beta$ adrenergic receptor blockade abolished the rise in BP and HR caused by leptin infusion.
Inhibition of nitric oxide synthesis with L-NAME enhances leptin-induced hypertension and tachycardia

Impaired nitric oxide formation amplifies the hypertensive effects of leptin
Leptin deficient mice are severely obese and exhibit many features of metabolic syndrome.

WT Ob -/-

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Despite severe obesity leptin deficient mice do not have elevated BP

![Image of WT and Ob -/- mice]

Telemetry - 5 days average

**MAP (mmHg)**

WT

Ob -/-

**Hypertension, 52: e104, 2008**

do Carmo JM, da Silva AA and Hall JE.
Humans with leptin deficiency are markedly obese

Humans with leptin gene mutations are not hypertensive despite early onset obesity and metabolic syndrome

**Results:** 4 patients with homozygous missense mutations of the leptin gene all had early onset morbid obesity and
- **severe insulin resistance, hyperinsulinemia**
- **dyslipidemia**
- **decreased sympathetic activity, postural hypotension**
- **decreased renin-angiotensin-aldosterone system response to upright posture**
- **no hypertension**

**Note:** All subjects studied were young, with early onset obesity.

Ozata M et al. *J Clin Endocrinol Metab* 84: 3686-95, 1999
Leptin appears to be an important link between obesity, sympathetic activation and hypertension in humans as well as in rodents.
Potential brain mechanisms by which leptin regulates appetite and sympathetic activity: role of the melanocortin system
MC4R deficient mice are obese and exhibit many features of metabolic syndrome

MC4R deficient mice are not hypertensive and are resistant to the hypertensive effects of leptin

Humans with MC4R deficiency exhibit marked early onset obesity, but have normal to low BP and reduced SNS activity

- Appetite
- Insulin resistance
- Insulin
- Leptin
- Dyslipidemia
- Blood pressure
- Sympathetic Activity

Greenfield JR et al.  
BP, 24-hr urinary NE excretion and hypertension prevalence are lower in obese MC4R deficient subjects than obese controls.
Activation of the CNS melanocortin system (e.g., activation of MC4R) appears to be necessary for obesity and hyperleptinemia to raise SNA and BP.
Blockade of MC4R causes a greater reduction in BP in SHRs compared to Wistar rats

Potential brain mechanisms by which leptin regulates appetite and sympathetic activity: role of the melanocortin system.
Generation of mice with selective leptin receptor deletion in proopiomelanocortin (POMC) neurons

LepR<sub>flox/flox</sub> x POMC/Cre

- Cre

Transcription

Floxed lepR gene

mRNA encoding defective protein

Normal mRNA

LepR<sub>flox/flox</sub>

POMC Specific LepR KO
Leptin receptor deletion in POMC causes only modest obesity when compared to leptin receptor deletion in the entire CNS.
Leptin receptor deletion in POMC completely abolished leptin’s ability to raise BP
Mice with leptin receptor deletion in POMC neurons exhibit markedly attenuated BP and HR responses to acute air jet stress

do Carmo JM et al.  
*Hypertension* 57: 918-26, 2011
Leptin receptors in POMC neurons are critical for leptin’s ability to raise BP, but are not an important component of the appetite suppressing action of leptin. This suggests that CNS effects of leptin may be differentially regulated.
Leptin receptor signaling

- **Blood pressure regulation?**
  - Jak2
  - PI3K
  - Irs2

- **Thermogenesis, Glucose regulation?**
  - Jak2
  - PI3K
  - Tyr985
  - Shp2
  - MAPK

- **Appetite**
  - Jak2
  - PI3K
  - Tyr1138
  - STAT3
Does deletion of IRS2 signaling in POMC neurons attenuate or abolish the hypertensive effects of leptin?
Mice with IRS2 deletion in POMC neurons have similar body weight and food intake compared to control mice

Unpublished observation (manuscript in preparation)
IRS2 deletion in POMC neurons did not abolish the effect of leptin to decrease food intake.

Unpublished observation (manuscript in preparation)
IRS2 deletion in POMC neurons did not attenuate the effect of leptin to reduce plasma glucose and insulin levels.

Glucose (mg/dl)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Leptin</th>
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<tbody>
<tr>
<td>IRS2&lt;sup&gt;flox/flox&lt;/sup&gt; (n=9)</td>
<td>160</td>
<td>120</td>
</tr>
<tr>
<td>IRS2-POMC (n=9)</td>
<td></td>
<td></td>
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Insulin (µU/ml)

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<thead>
<tr>
<th></th>
<th>Control</th>
<th>Leptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRS2&lt;sup&gt;flox/flox&lt;/sup&gt; (n=9)</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>IRS2-POMC (n=9)</td>
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</tr>
</tbody>
</table>

* p<0.05 compared to control period

Unpublished observation (manuscript in preparation)
IRS2 deletion in POMC neurons abolished the chronic blood pressure effects of leptin

Unpublished observation (manuscript in preparation)
The IRS2 signaling pathway in POMC neurons plays a major role in mediating the effects of leptin on BP, but not on appetite or glucose homeostasis.
Leptin reverses the decrease in heart rate caused by uncontrolled diabetes

MC3/4-R antagonism prevented leptin’s effect to raise heart rate back to control values in diabetic rats.
$\alpha_1/\beta_{1,2}$ adrenergic blockade attenuated $\sim 50\%$ of leptin’s effect to raise heart rate in diabetic rats

Leptin increases sympathetic input to the heart of diabetic rats

Leptin increases intrinsic heart rate of diabetic rats back to pre-diabetic values

Leptin restored baroreflex sensitivity in diabetic rats back to control values

Tachycardia

\[ \begin{align*}
C & - 3.2 \pm 0.5 \\
D & - 1.9 \pm 0.3 \quad \star \\
L & - 3.4 \pm 0.3
\end{align*} \]

Bradycardia

\[ \begin{align*}
C & - 2.6 \pm 0.3 \\
D & - 1.7 \pm 0.3 \quad \star \\
L & - 3.4 \pm 0.5
\end{align*} \]

\* p<0.05 vs control

Chronic infusion of glucose was able to maintain hyperglycemia during ICV leptin treatment.

**Graph:**
- **X-axis:** Days
- **Y-axis:** Blood Glucose (mg/100ml)
- **Legend:**
  - Glucose (35% - 1.7 ml/hr, IV)
  - Leptin (0.02 μg/kg/min, ICV)
  - Induction of Diabetes (STZ - 50 mg/kg)

**References:**
Infusion of glucose to maintain hyperglycemia did not prevent leptin’s effect to raise heart rate in diabetic rats

Induction of Diabetes (Streptozotocin 50 mg/kg)

Leptin (0.02 µg/kg/min, ICV)

Glucose (35% - 1.7 ml/hr, IV)

Take Home Messages

• Obesity is the leading cause of essential hypertension (caused by several mechanisms including sympathetic activation).

• The increased leptin levels in obesity appear to be a key link between obesity, sympathetic activation and hypertension.

• Activation of the brain melanocortin system is necessary for the development of obesity-hypertension and for leptin to exert its hypertensive effects.
Take Home Messages

• Activation of the **IRS2 signaling pathway in POMC neurons** is important for the BP effects of leptin but not for the appetite and metabolic actions of leptin.

Understanding the CNS mechanisms by which the leptin-melanocortin system differentially regulates appetite, glucose homeostasis and cardiovascular function may reveal new targets for therapies with greater efficacy and less side-effects to treat obesity.
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