mTORC1 is required for leptin-induced sympathetic activation to the kidney but not brown adipose tissue

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FINANCIAL DISCLOSURE:
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UNLABELED / UNAPPROVED USES DISCLOSURE:
No unlabeled / unapproved uses to disclose.
Obesity represents a major global health epidemic and increases cardiovascular risk.

Leptin has emerged as a critical link between obesity and hypertension.
Leptin signals energy reserve status and increases sympathetic nerve activity (SNA).

↑ Cardiovascular SNA

↑ Energy Expenditure

↓ Food Intake

↑ Blood Pressure

↑ Adipose Tissue

↓ Food Intake

Leptin
Leptin activates regional sympathetic outflow

Do unique molecular pathways underlie leptin-evoked sympathetic activation to the BAT and kidney?

Leptin action at its receptor activates multiple downstream signaling cascades.

- Leptin activates the JAK2-STAT3 and PI3K-AKT/mTOR pathways.
- PI3K leads to the activation of S6K and mTOR, which in turn activates S6.
- JAK2-STAT3 activation is inhibited by Rapamycin, which reduces food intake and body weight.
- Leptin also activates the STAT5 pathway, which is involved in blood pressure regulation.

**References:**
- Cota, Science 2006
- Harlan, Cell Metab. 2013
- Cota, Science 2006
Hypothesis:

mTORC1 signaling differentially controls the regional sympathetic effects of leptin to metabolic and cardiovascular regulatory tissues
Experimental Design

C57 → LepRb\textsuperscript{Cre} \times Raptor\textsuperscript{fl/fl} → LepRb\textsuperscript{Cre} Raptor\textsuperscript{fl/fl} → ICV rapamycin pretreatment → Regional sympathetic nerve responses to ICV leptin
mTORC1 inhibition by rapamycin selectively inhibits renal but not BAT sympathetic responses to leptin.

Δ Renal SNA (%)

Δ BAT SNA (%)

n=5-6, * p<0.05
Experimental Design

C57

ICV rapamycin pretreatment

Regional sympathetic nerve responses to ICV leptin

LepRb\textsuperscript{Cre}

Raptor\textsuperscript{fl/fl}

\texttimes

LepRb\textsuperscript{Cre}

Raptor\textsuperscript{fl/fl}
Deletion of Raptor from leptin receptor expressing cells prevents leptin-induced S6 but not STAT3 phosphorylation
Deletion of Raptor from leptin receptor expressing cells prevents leptin-induced S6 but not STAT3 phosphorylation.
Mice lacking mTORC1 in leptin receptor expressing cells have impaired renal but not BAT sympathetic responses to leptin

Δ Renal SNA (%)  
Δ BAT SNA (%)

n=4-7, * p<0.05
Baseline body weight and food intake are not altered in LepRb$^{Cre}$/Raptor$^{floxfloxt}$ mice.
LepRb$^{Cre}$/Raptor$^{flox/flox}$ mice exhibit a normal food intake and body weight response to i.p. leptin.
Mean arterial pressure response to ICV leptin (2µg) is blunted in LepRb<sup>Cre</sup>/Raptor<sup>flox/flox</sup> mice. n=3, * p<0.05 vs. baseline.
Conclusions

Central mTORC1 signaling and specifically mTORC1 in leptin receptor expressing cells is required for leptin-induced sympathoexcitation to the kidney but not brown adipose tissue.

mTORC1 likely plays an important role in mediating leptin’s effects on blood pressure but not metabolism.
Working Model: mTORC1 uncouples the regional sympathetic effects of leptin
mTORC1 may represent an important mediator of the preserved cardiovascular actions of leptin during obesity
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Obesity represents a major global health concern and increases cardiovascular risk. Inappropriate leptin action is implicated in the pathophysiology of both obesity and hypertension.
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Leptin has emerged as a critical link between obesity and hypertension.

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