Central control of metabolism by thyroid hormone

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Nothing to disclose
Learning objectives

1. Thyroid hormones regulate energy balance and metabolism by acting at central level
2. Thyroid hormones modulate the autonomous nervous system
3. Thyroid hormones modulate hypothalamic energy sensors to regulate feeding
4. Thyroid hormones modulate hypothalamic energy sensors to regulate thermogenesis in BAT
5. Thyroid hormones act on the hypothalamus to regulate hepatic glucose metabolism
6. Thyroid hormones act on the hypothalamus to regulate cardiac function
Central regulation of energy balance


PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Miguel Lopez)
Hypothalamic regulation of energy balance and metabolism

Brain

Hypothalamus

Hormonal and nutritional signals

Liver
Beta-cell (pancreas)
Skeletal muscle
WAT
BAT

Food intake

Autonomic Nervous System

Orexigenic neuropeptides (AgRP, NPY, MCH, OXs)
Anorexigenic neuropeptides POMC (α-MSH), CART

Glucose and lipid metabolism

Energy expenditure

Hypothalamic AMPK: a whole body metabolic gauge

LKB1 → TAK1 → CaMKKβ → PP2Cα

Ca²⁺ → Thr172

Cidea

AMPK

Cellular level

ATP-consuming processes

Energy expenditure

Whole body level

ATP-producing processes

Energy production (i.e. Food intake)


PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Miguel Lopez)
Hypothalamic AMPK modulates food intake


Hypothalamic AMPK modulates BAT thermogenesis

PT1B1: Protein tyrosine phosphatase 1B (attenuates leptin signaling by dephosphorylating JAK2)

Central regulation of BAT thermogenesis

Whittle A et al (2012). TMM. 17:405-411
Central thyroid hormones and BAT thermogenesis
Classical peripheral view of thyroid thermogenesis

Thyroid hormones induce BAT thermogenesis

Could thyroid-induced thermogenesis be regulated at central level?

The Interaction between Thyroid and Brown-Fat Thermogenesis
Central or Peripheral Effects?

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TRα1 aporeceptor mice

“Functional blockage (30 °C) of sympathetic signaling to BAT normalizes the metabolic phenotype. Thus central signaling overrides peripheral action on thyroid hormones”

Does hypothalamic AMPK mediate thyroid-induced thermogenesis in BAT?
Central T3 inhibits hypothalamic AMPK and induces BAT thermogenesis


Body weight change (g) vs Time (d): Vehicle ICV vs T3 ICV

Food intake (g) vs Time (d): Vehicle ICV vs T3 ICV

Protein levels/β-actin (% vehicle)
- pAMPKα
- AMPKα1
- AMPKα2
- pACCα
- ACCα

mRNA levels/Hprt (% vehicle)
- UCP1
- UCP3
- PGC1α
- PGC1β

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PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Miguel Lopez)
Stereotaxic administration in VMH and ARC

VMH

85-90%

ARC

75-80%
T3 in the VMH induces BAT thermogenesis and weight lost

(no changes in the ARC were found)
T3 in the VMH inhibits AMPK signalling

T3 in the VMH activates SNS

ΔΔΔΔ

BAB SNA (%)

-50
0
50
100
150
200
250
300

0 45 90 135 180 225 270 315 360

Time (min)

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PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Miguel Lopez)
New model of central T3 actions on energy balance

BMP8B induces BAT thermogenesis through AMPK in the VMH

Nicotine induces BAT thermogenesis through AMPK in the VMH

Martínez de Morentin PB et al (2012). Diabetes 61:807-817
The hypothalamic AMPK-BAT axis: a canonical mechanism

- Peripheral and central signals
  - SNS
  - Hypothalamus
  - 3V
  - RPa
  - IO
  - VMH
  - β3-AR
  - BAT

- Energy expenditure
  - Ucp1
  - Ppargc1a
  - Ucp3
  - Ppargc1b

- Body weight

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Miguel Lopez)
Central thyroid hormones and food intake
Hypothalamic mTOR: a whole body energy sensor


PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Miguel Lopez)
T3 in the ARC induces food intake

**Figure 1:**

- **VMH**
  - Vehicle VMH
  - T3 VMH

- **ARC**
  - Vehicle ARC
  - T3 ARC

**Graphs**

**Food intake (g)**

**References**

T3 in the ARC induces mTOR signalling

New central view of thyroid hormones actions on energy balance

Central thyroid hormones and glucose homeostasis
T3 in the PVH induces hepatic glucose production through SNS


(effect independent of plasma T3, insulin, glucagon and CORT)
Energy balance regulation by thyroid hormones at central level

- Thyroid gland
- Energy expenditure
- Body weight
- BAT
- Food intake
- AMPK
- VMH
- 3V
- ARC
- mTOR
- NP
- Y
- AgR
- POMC
- β3-AR
- PVH
- Complex lipids?
- Malonyl-CoA?
- AMPK?
- mTOR?
- DMV
- PSNS (vagus nerve)
- SNS
- PVH
- AMPK?
Central thyroid hormones and cardiovascular function
Central T3 modulates cardiovascular function

Forrest & West (2013). JCI 123: 117-120
“Take home message”

Thyroid hormones act within the hypothalamus to modulate energy balance, metabolism and cardiovascular function through the autonomous nervous system.
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