USC
UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Department of Physiology

CiMUS
Centro Singular de Investigación en **Medicina Molecular** e **Enfermidades Crónicas**

NeurObesity Group

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Instituto de Investigación Sanitaria
SANTIAGO DE COMPOSTELA

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ciberobn

Central control of metabolism by thyroid hormone

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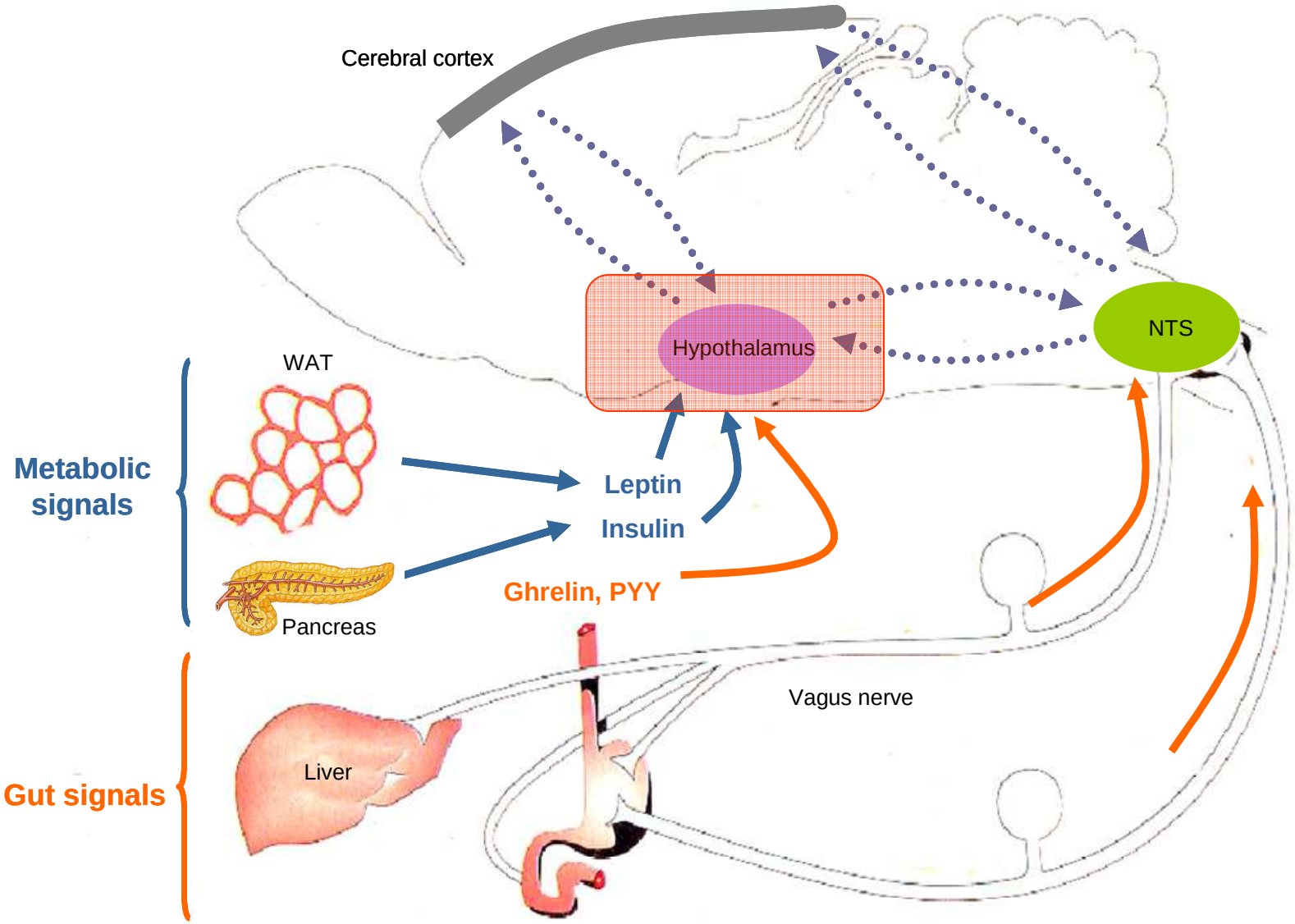
Disclosure

Nothing to disclose

Learning objectives

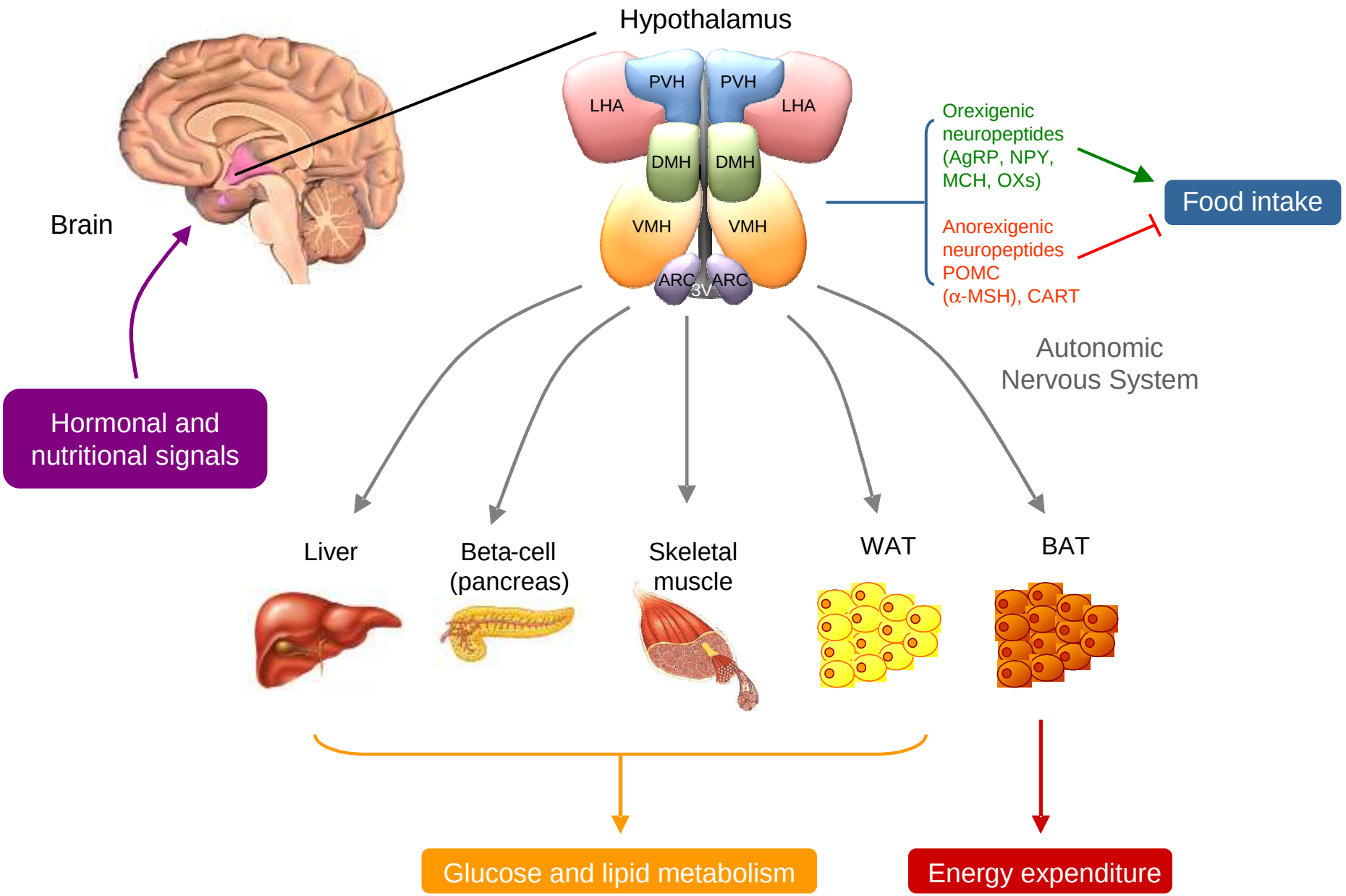
1. Thyroid hormones regulate energy balance and metabolism by acting at central level
2. Thyroid hormones modulate the autonomous nervous system
3. Thyroid hormones modulate hypothalamic energy sensors to regulate feeding
4. Thyroid hormones modulate hypothalamic energy sensors to regulate thermogenesis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

Central regulation of energy balance



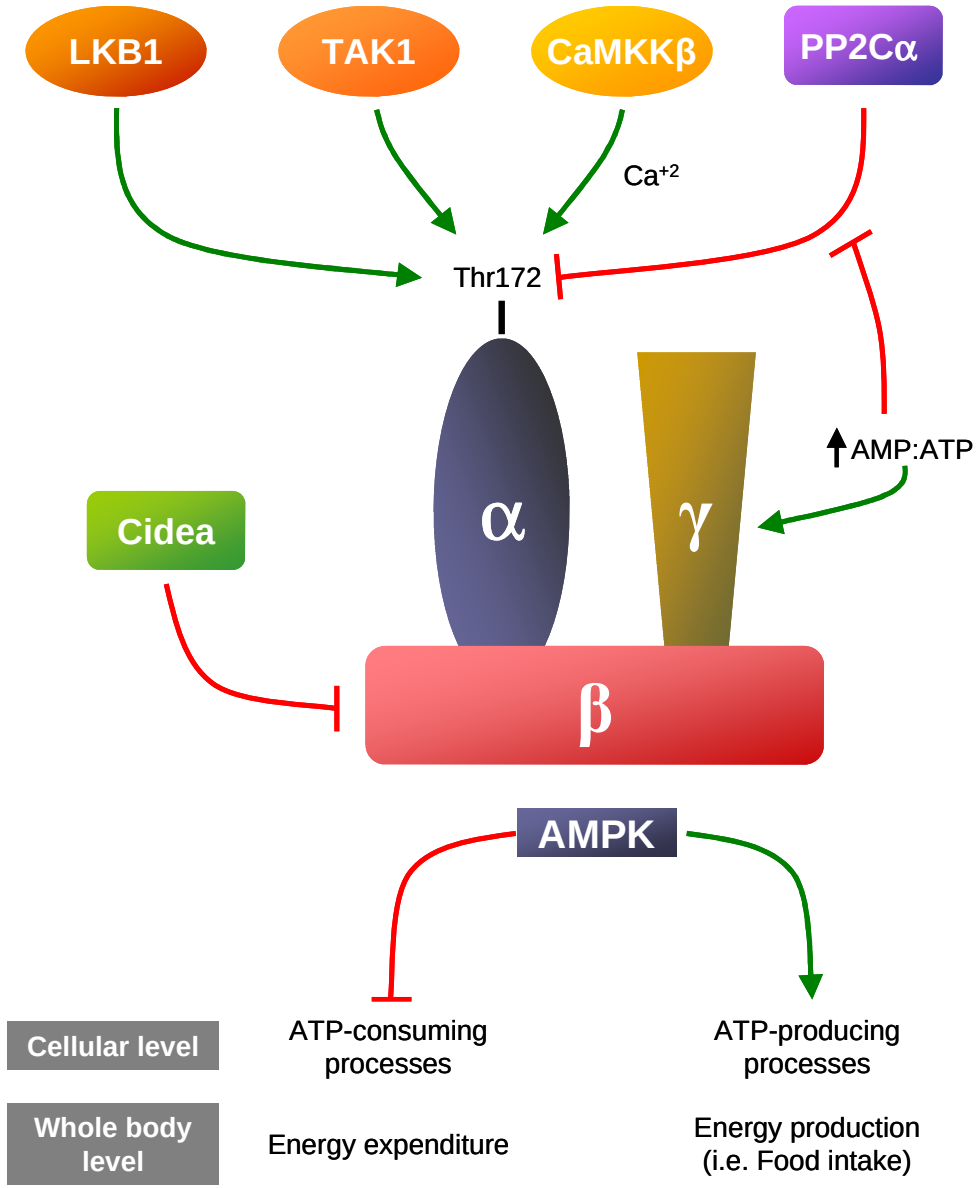
Modified from Schwartz M *et al* (2000). Nature 404:661-671

Hypothalamic regulation of energy balance and metabolism



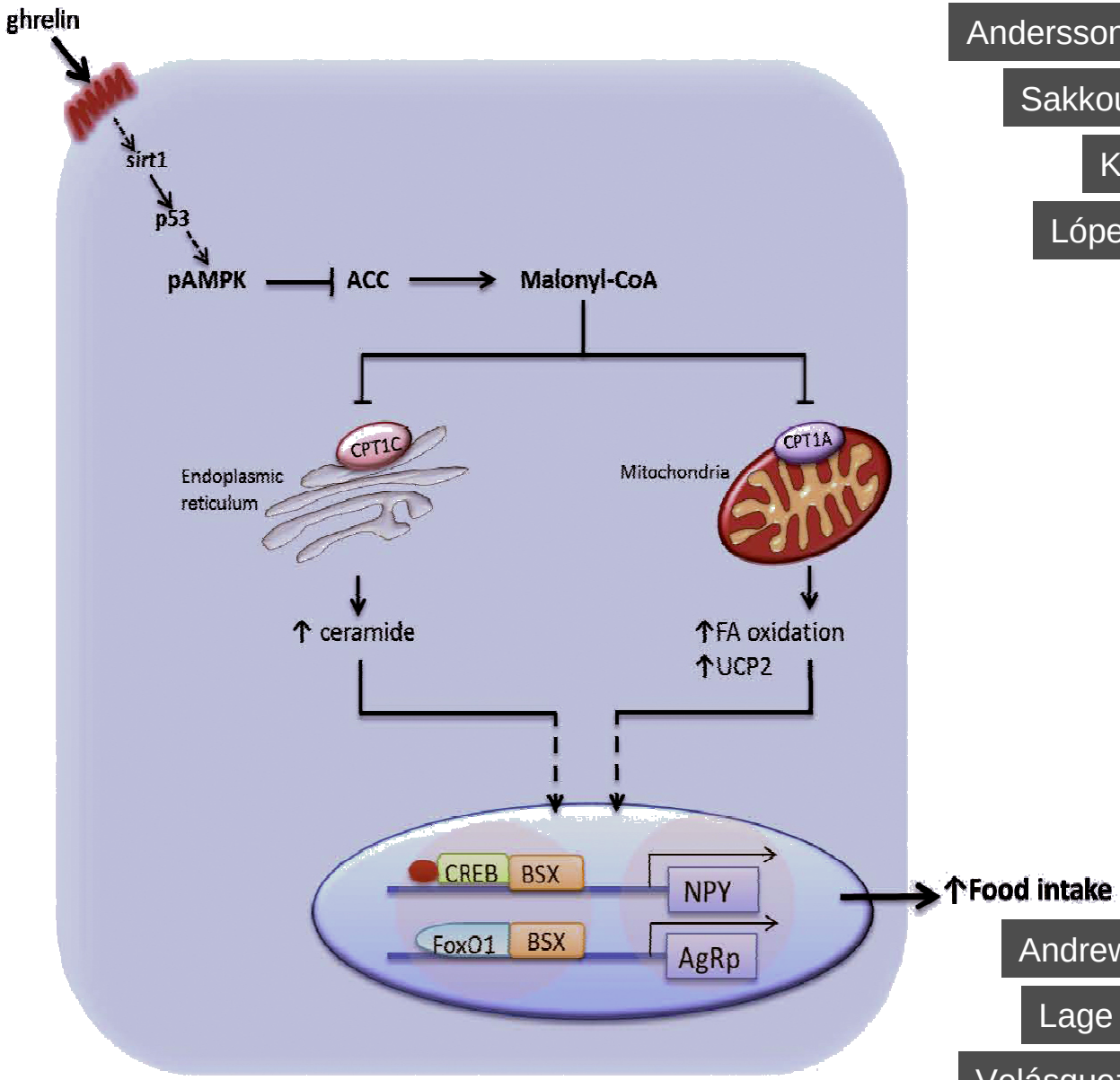
López *et al* (2013). TMM 19: 418-427

Hypothalamic AMPK: a whole body metabolic gauge



Lage R *et al* (2008) TMM 14:539-549

Hypothalamic AMPK modulates food intake



Andersson M *et al* (2004) JBC 279:12005-12008

Sakkou M *et al* (2007) Cell Metab 5, 450-463

Kola M *et al* (2008) PLoS ONE 3:e1797

López M *et al* (2008) Cell Metab 7:389-399

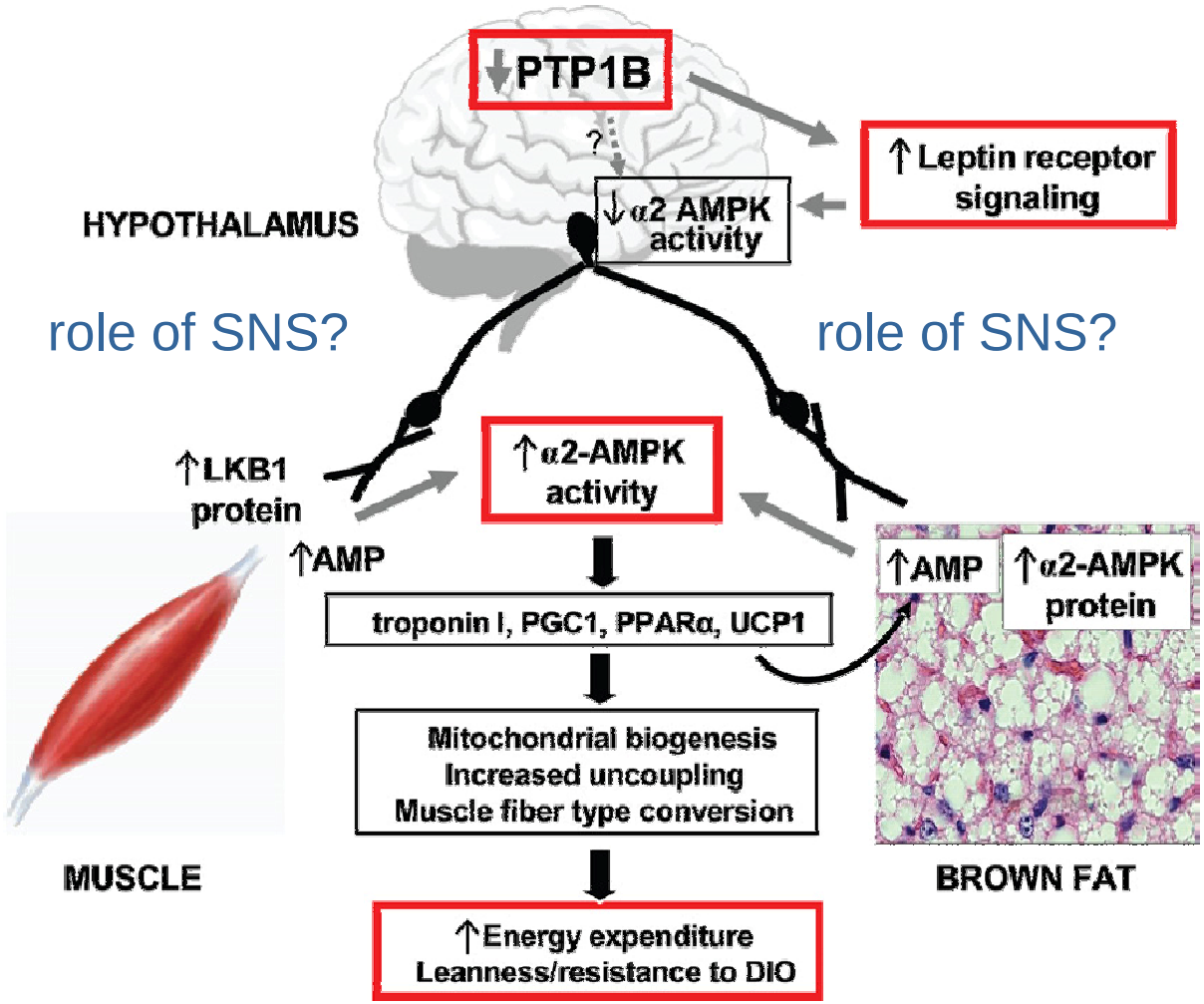
Andrews ZB *et al* (2008) Nature 454:846-851

Lage R *et al* (2010) FASEB J 24:2670-2679

Velásquez DA *et al* (2011) Diabetes 60:1177-85

Ramírez S *et al* (2013) Diabetes (in press)

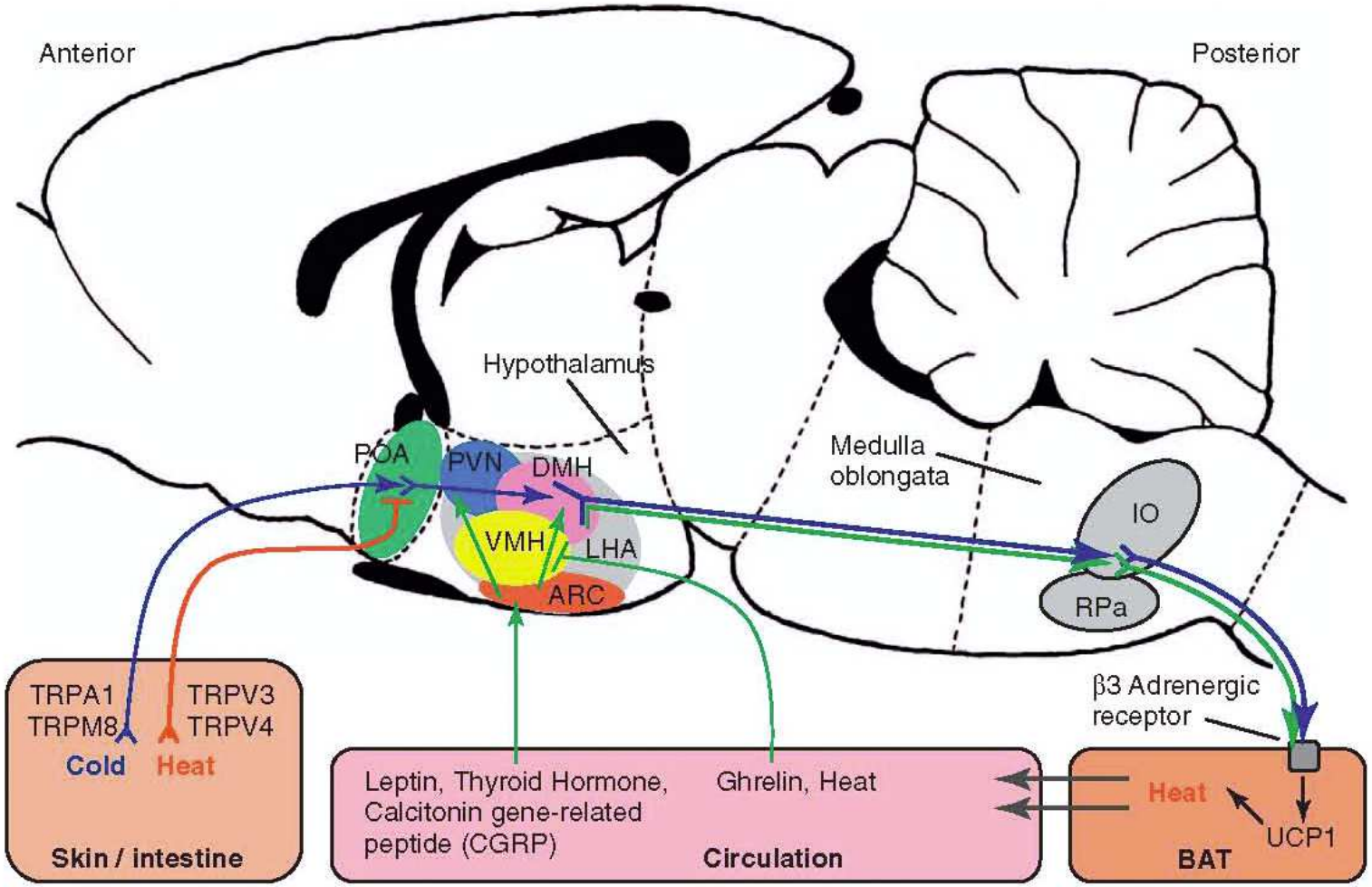
Hypothalamic AMPK modulates BAT thermogenesis



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

Xue B *et al* (2009). MCB 20:4563-4573

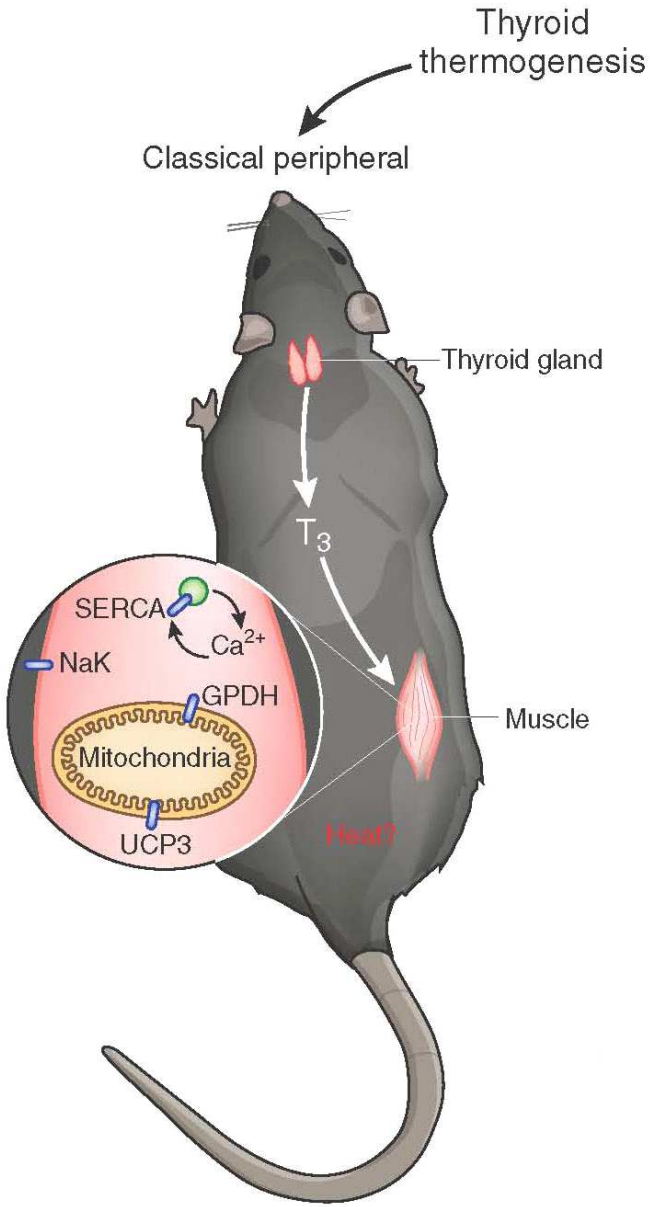
Central regulation of BAT thermogenesis



Whittle A *et al* (2012). TMM. 17:405-411

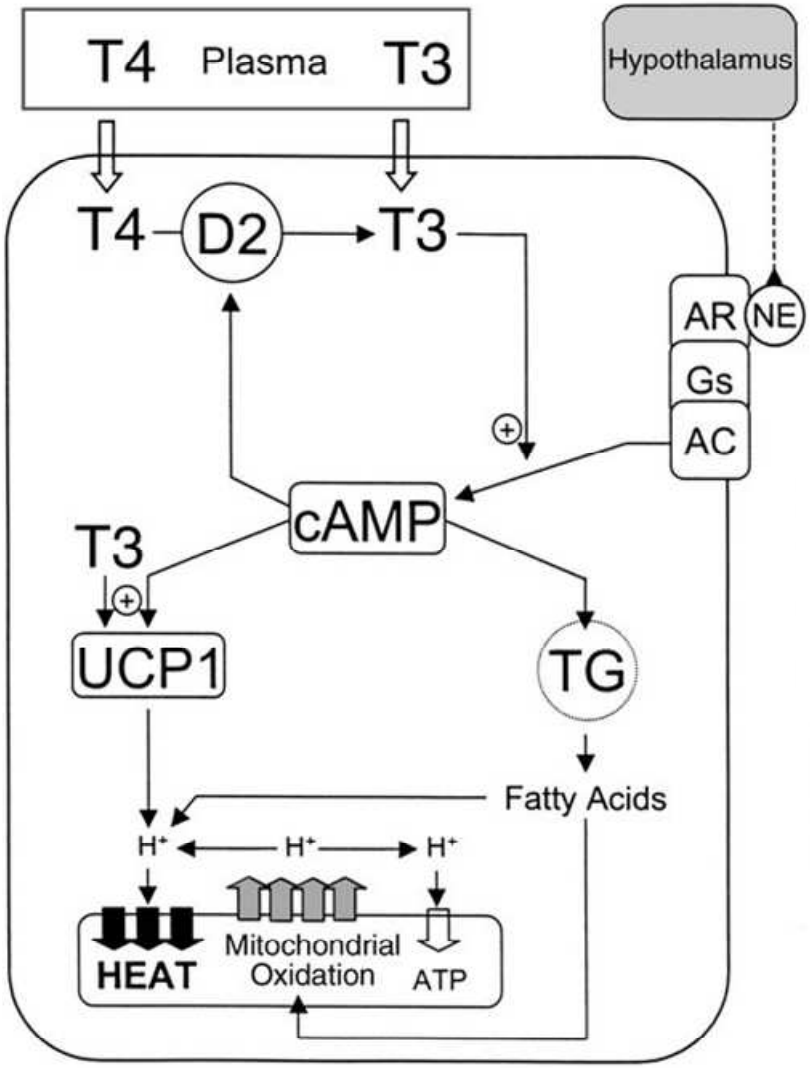
Central thyroid hormones and BAT thermogenesis

Classical peripheral view of thyroid thermogenesis



Cannon B & Nedergaard J (2010). Nat Med 16: 965-967

Thyroid hormones induce BAT thermogenesis



de Jesus LA *et al* (2001). JCI 108: 1379–1385

Central thyroid hormones and BAT thermogenesis

Could thyroid-induced thermogenesis be regulated at central level?

The Interaction between Thyroid and Brown-Fat Thermogenesis

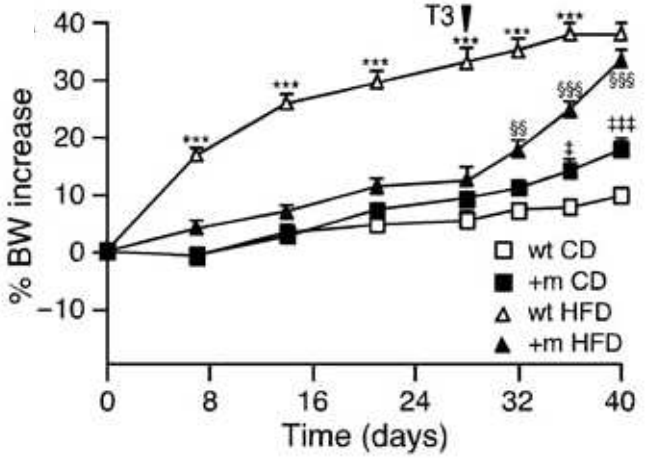
Central or Peripheral Effects?

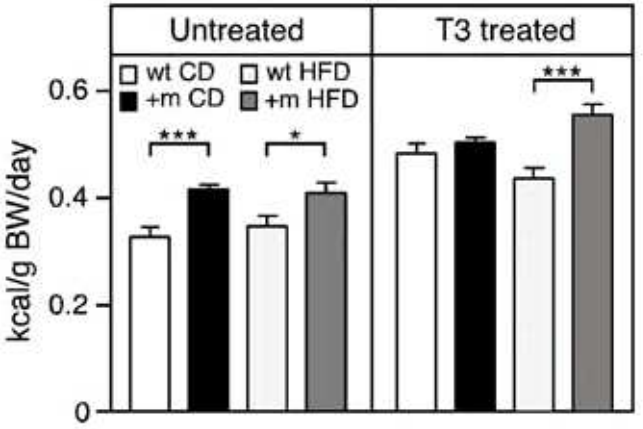
JAN NEDERGAARD,[a] ANDREA DICKER, AND BARBARA CANNON

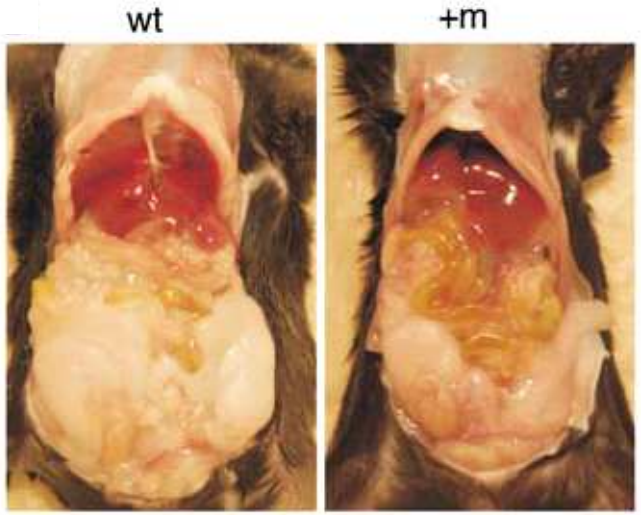
The Wenner-Gren Institute
The Arrhenius Laboratories F3
Stockholm University
S-106 91 Stockholm, Sweden

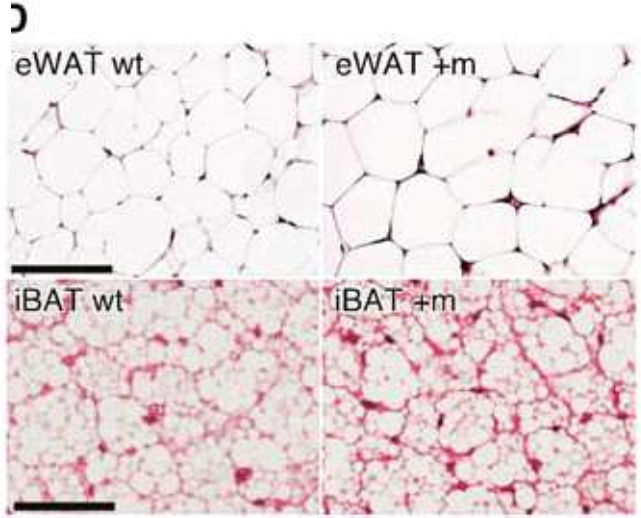
Nedergaard J *et al* (1997). Ann N Y Acad Sci. 15:712-7.

TRα1 aporeceptor mice





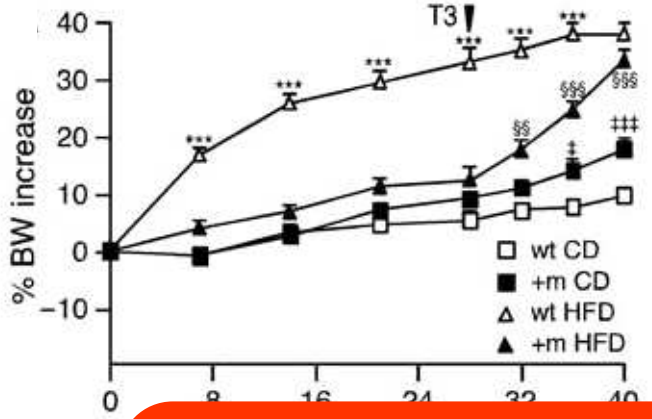


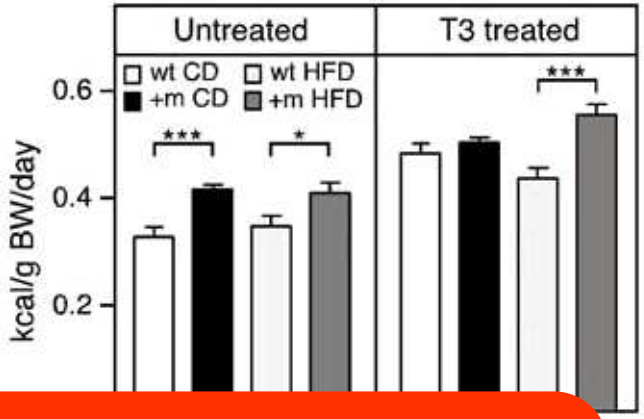


Sjögren *et al* (2007). EMBO J 26: 4535-4545

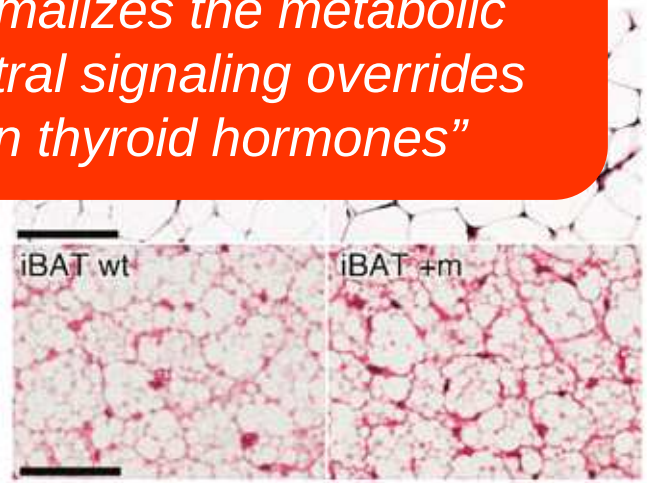
Warner *et al* (2013). PNAS 110: 16241–16246

TRα1 aporeceptor mice





"Functional blockage (30 ºC) of sympathetic signaling to BAT normalizes the metabolic phenotype. Thus central signaling overrides peripheral action on thyroid hormones"



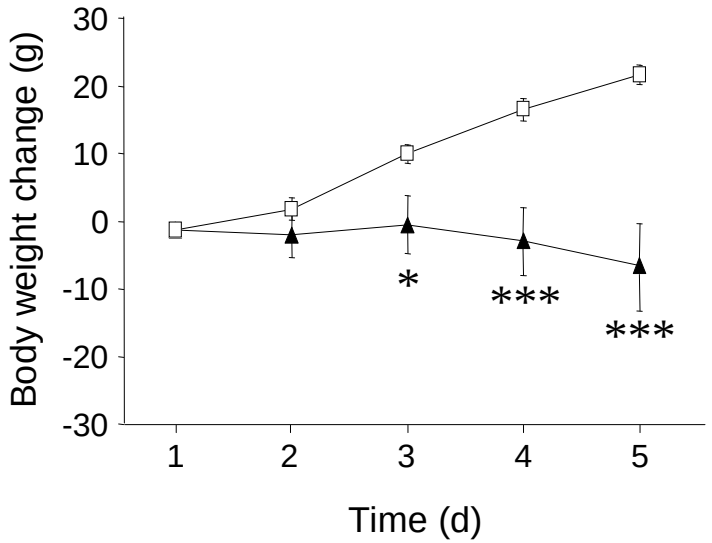
Sjögren *et al* (2007). EMBO J 26: 4535-4545

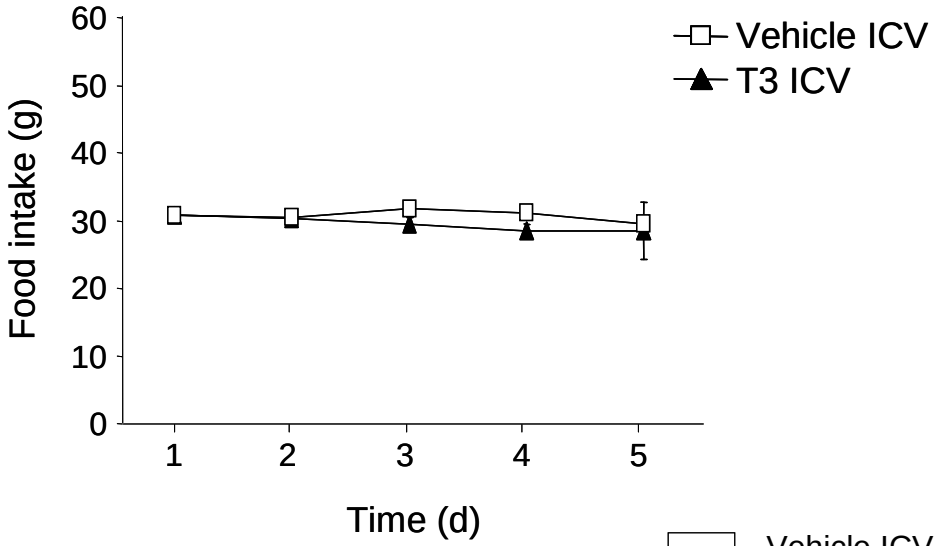
Warner *et al* (2013). PNAS 110: 16241–16246

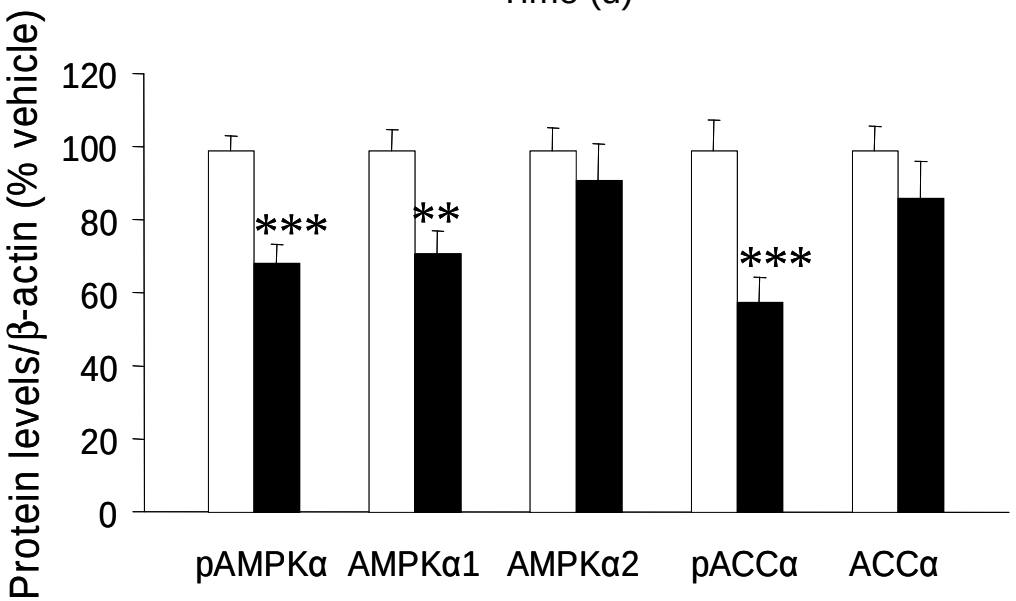
Hypothalamic AMPK, thyroid hormones and BAT thermogenesis

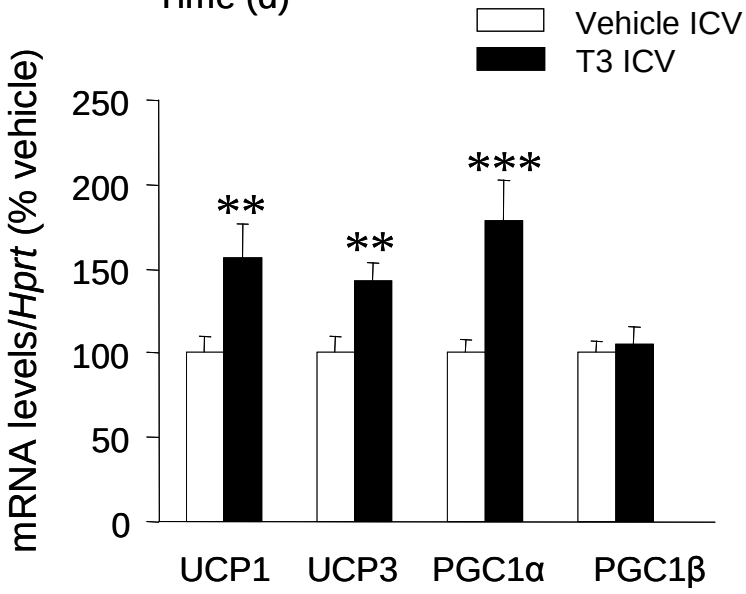
Does hypothalamic AMPK mediate thyroid-induced thermogenesis in BAT?

Central T3 inhibits hypothalamic AMPK and induces BAT thermogenesis





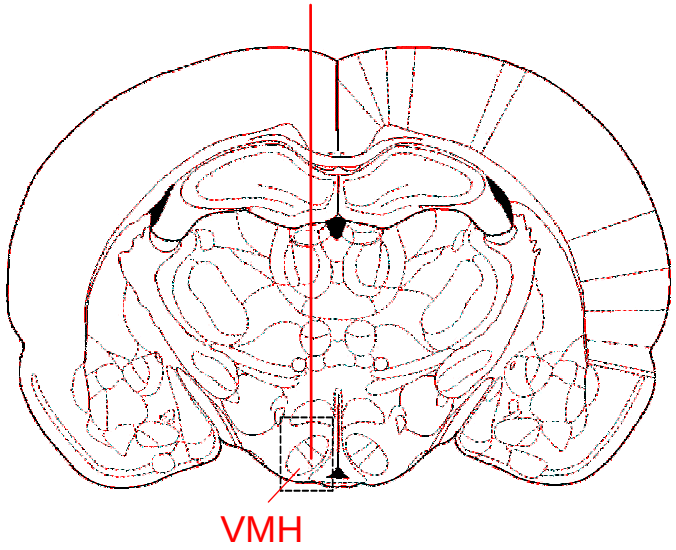


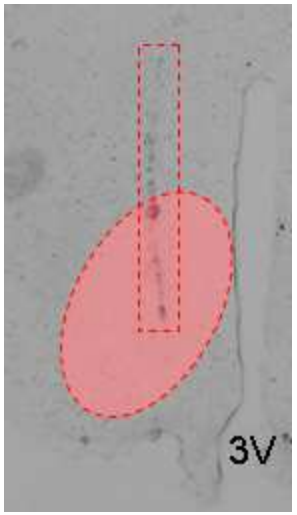


López M *et al* (2010). Nat Med 16: 1001-1008

Stereotaxic administration in VMH and ARC

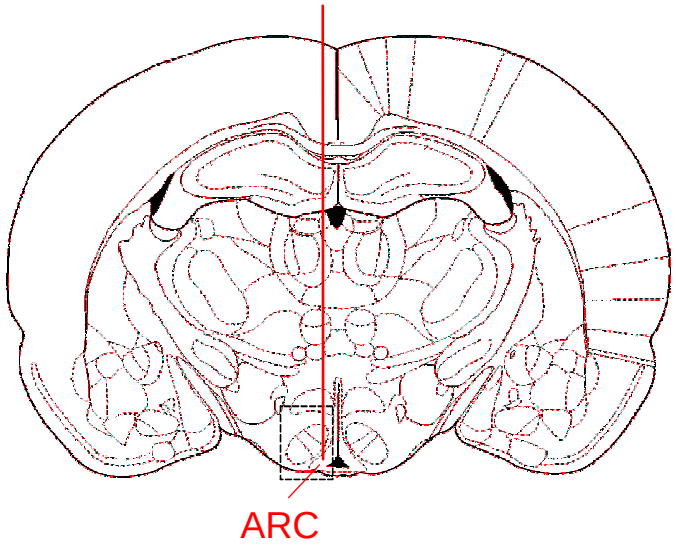
VMH

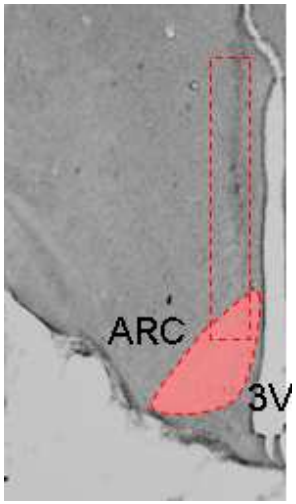




85-90%

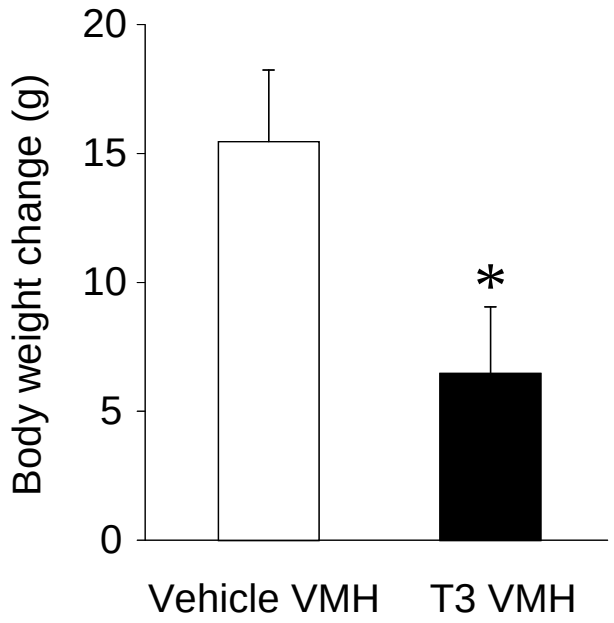
ARC

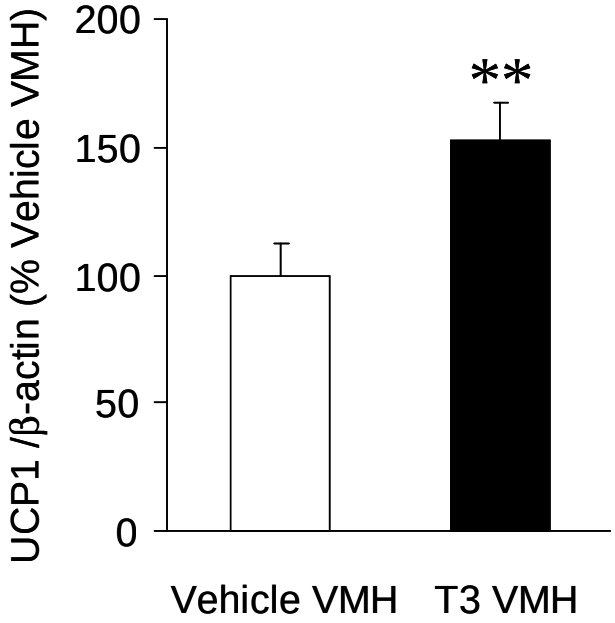




75-80%

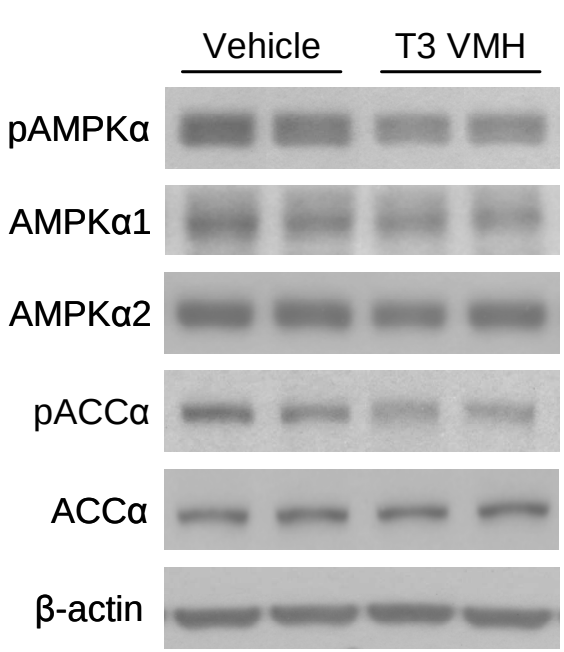
T3 in the VMH induces BAT thermogenesis and weight lost

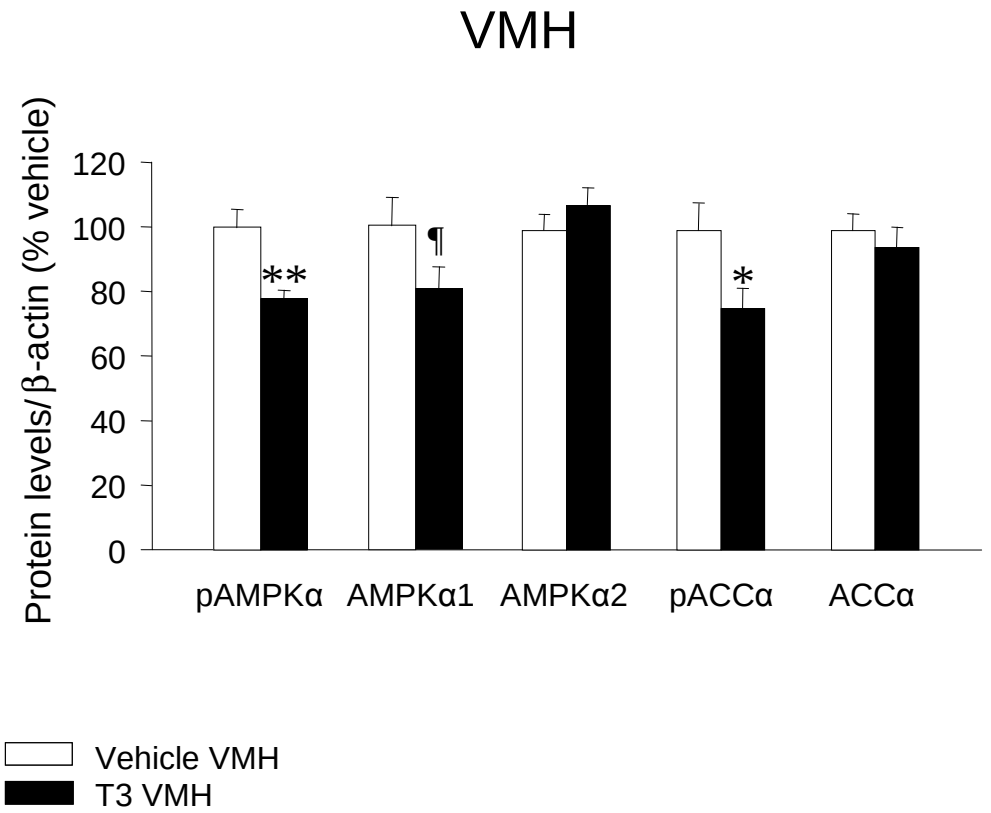




(no changes in the ARC were found)

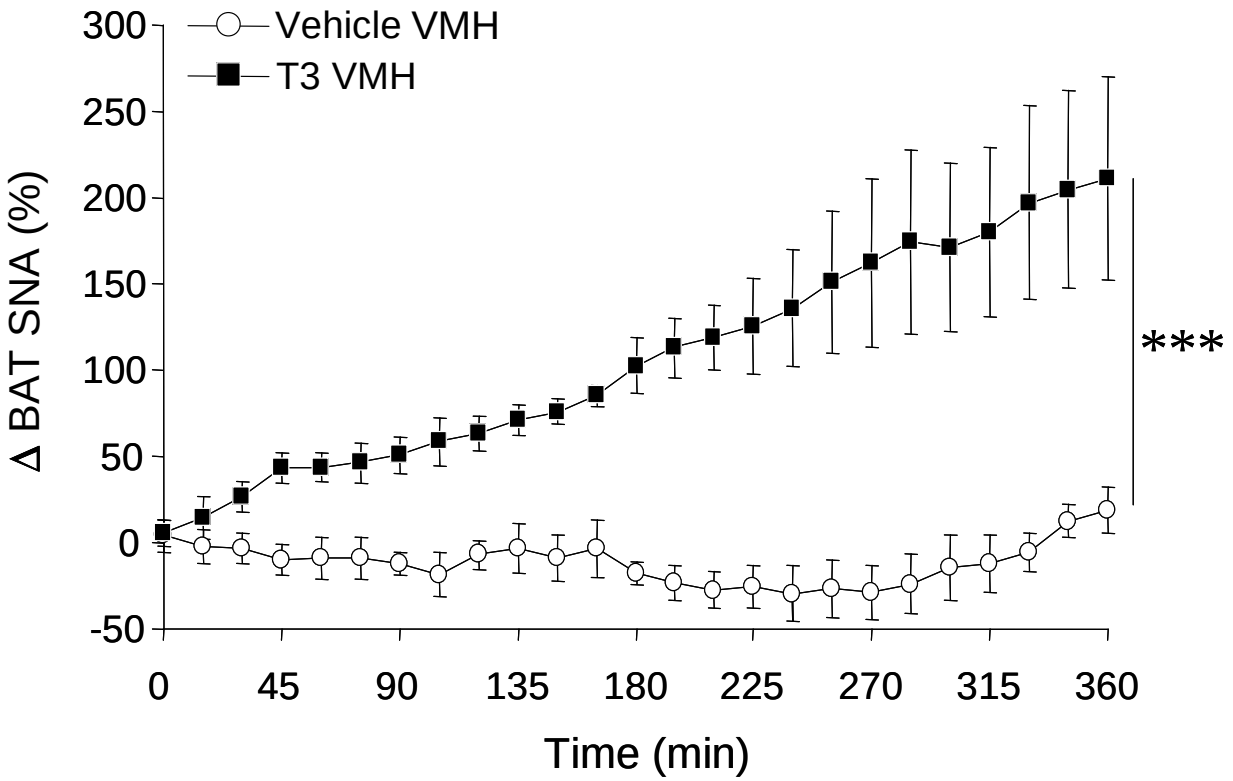
T3 in the VMH inhibits AMPK signalling





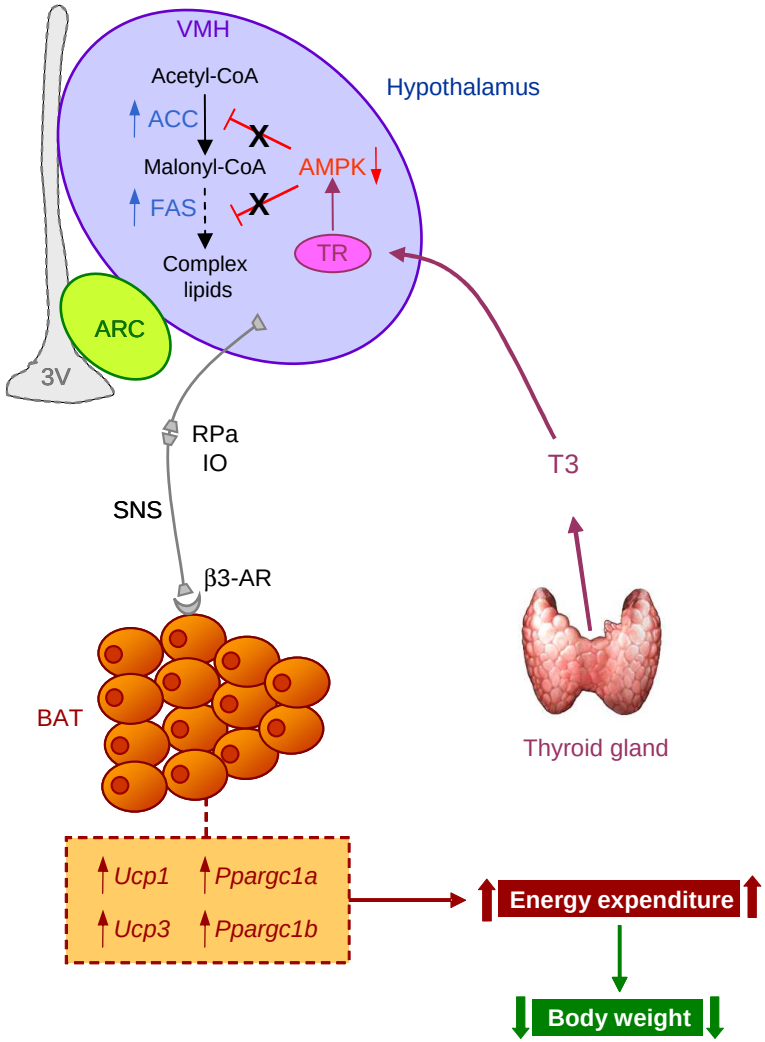
López M *et al* (2010). Nat Med 16: 1001-1008

T3 in the VMH activates SNS



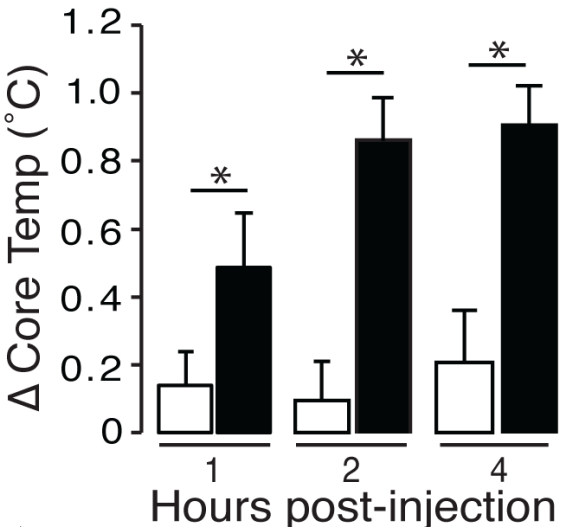
López M *et al* (2010). Nat Med 16: 1001-1008

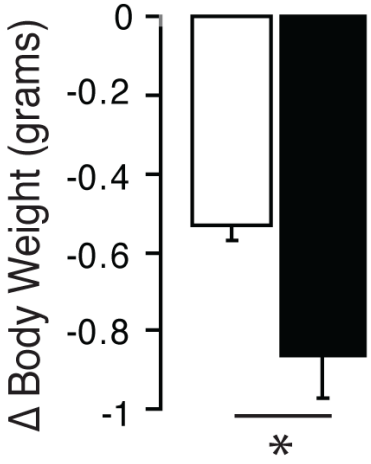
New model of central T3 actions on energy balance

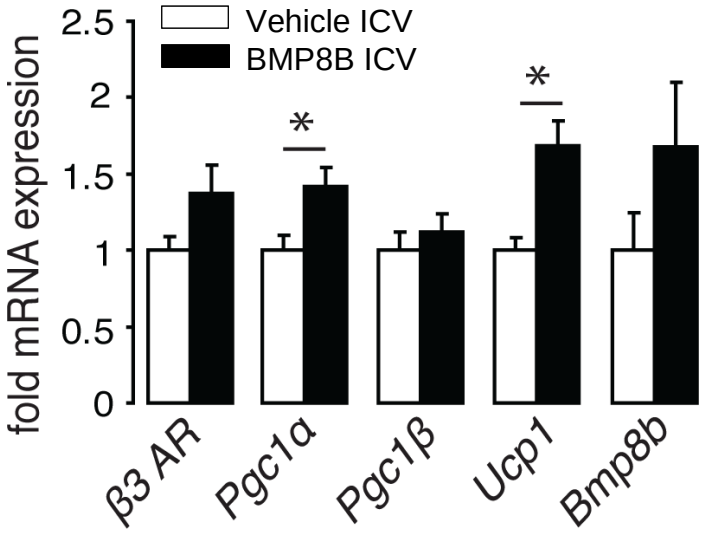


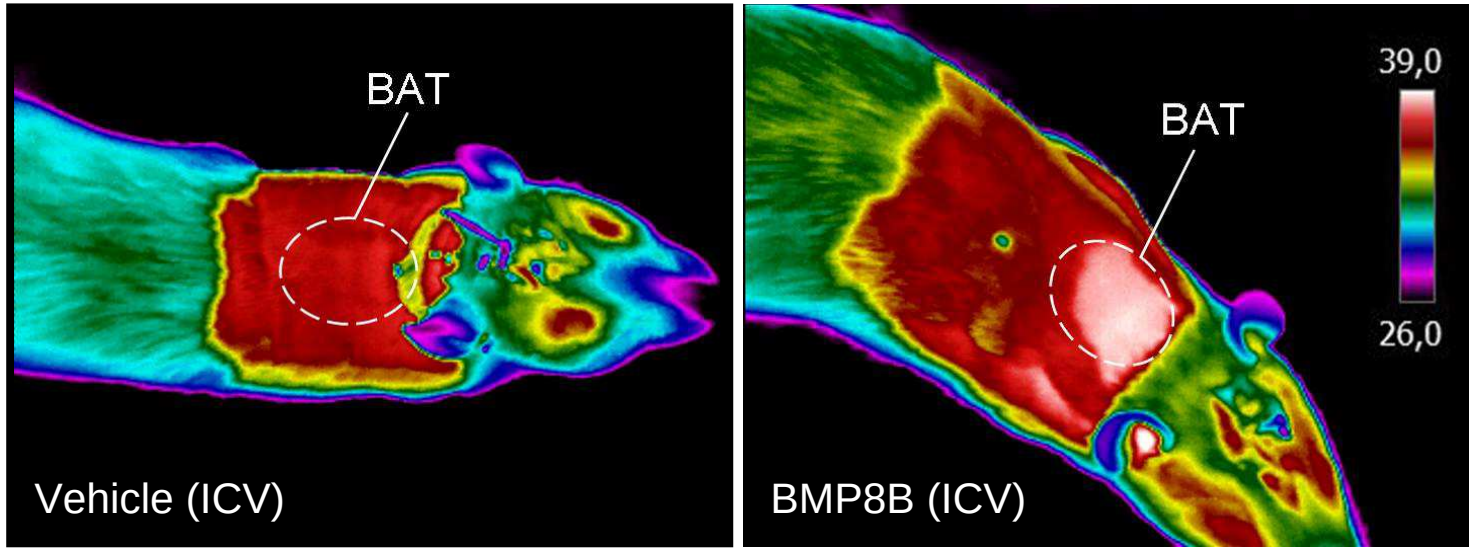
López M *et al* (2010). Nat Med 16: 1001-1008

BMP8B induces BAT thermogenesis through AMPK in the VMH



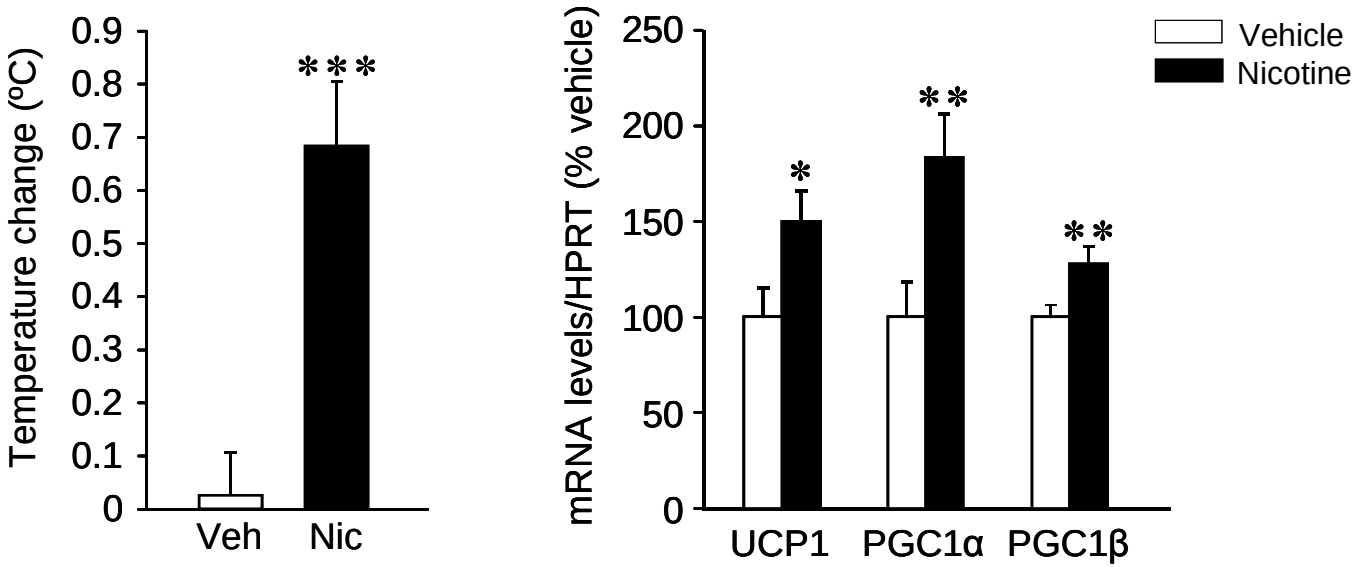






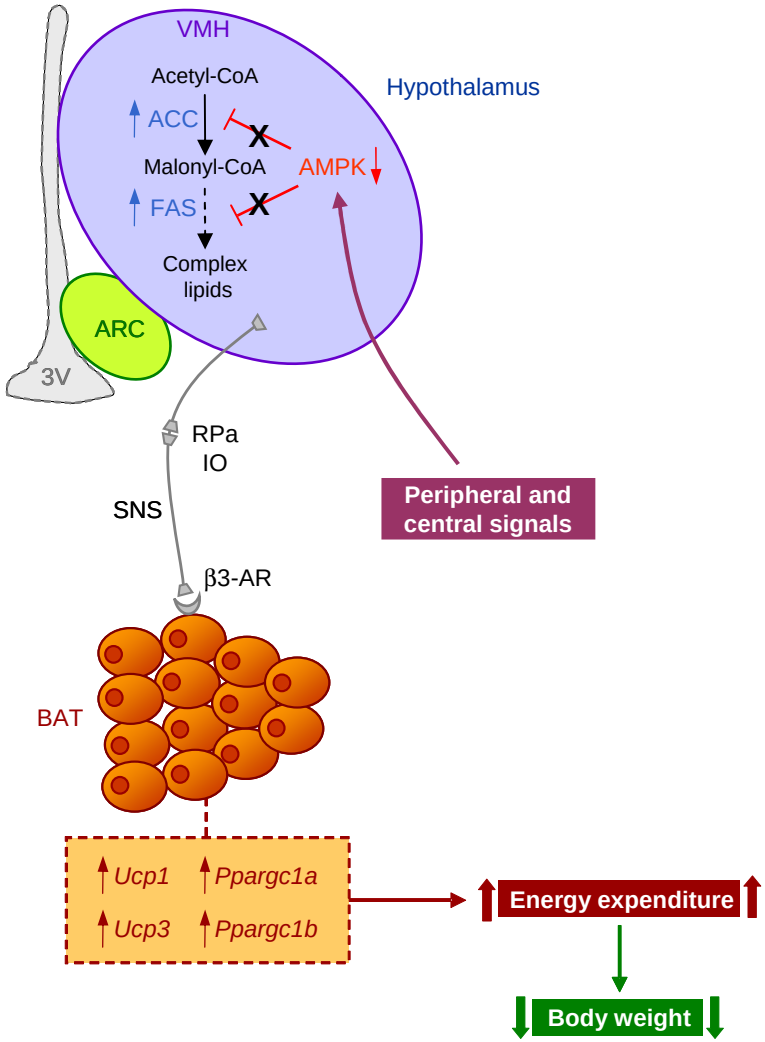
Whittle AJ *et al* (2012). Cell 149:871-885

Nicotine induces BAT thermogenesis through AMPK in the VMH



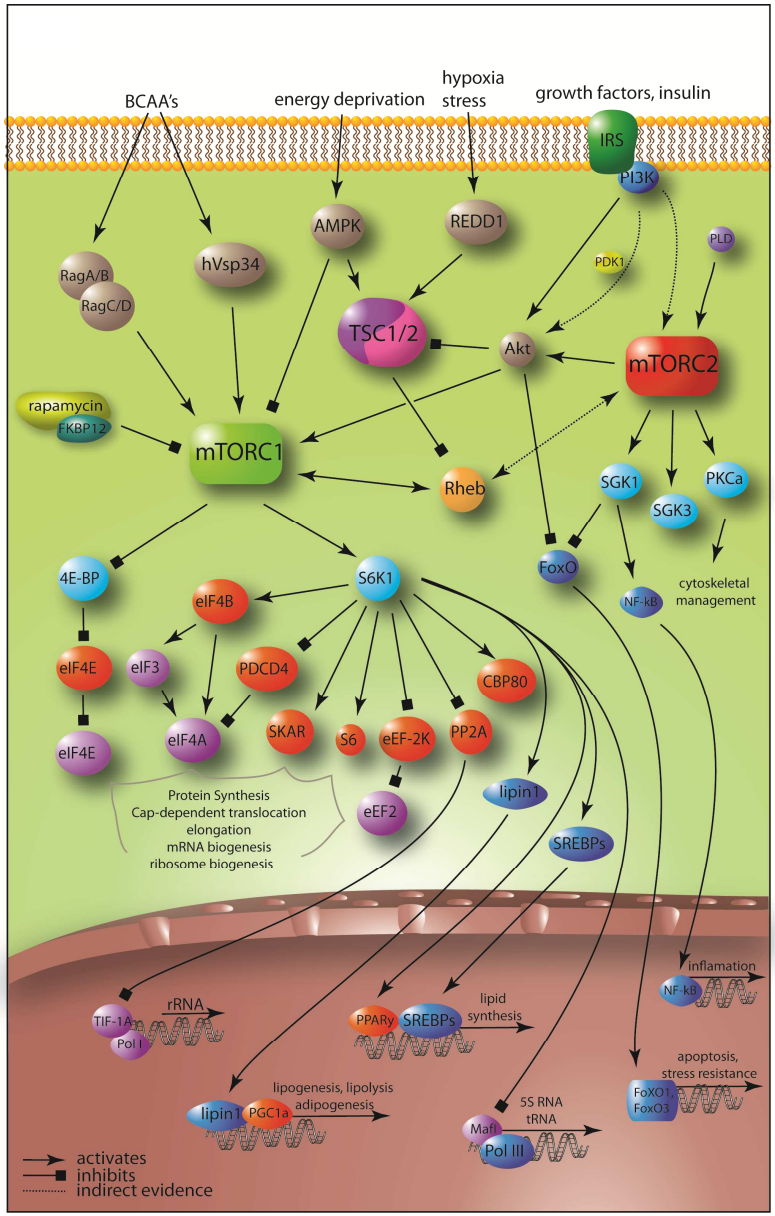
Martínez de Morentin PB *et al* (2012). Diabetes 61:807-817

The hypothalamic AMPK-BAT axis: a canonical mechanism



Central thyroid hormones and food intake

Hypothalamic mTOR: a whole body energy sensor



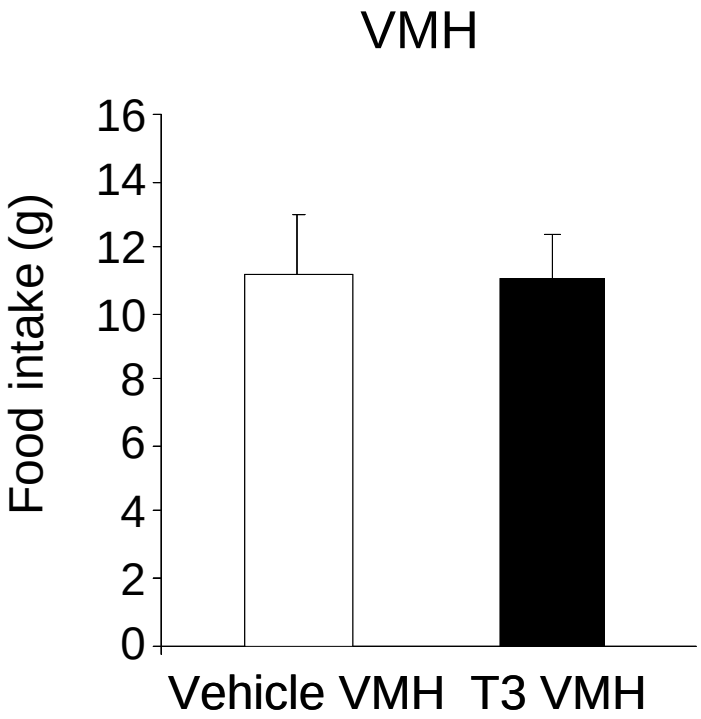
Cota D *et al* (2006). Science 312: 927-930

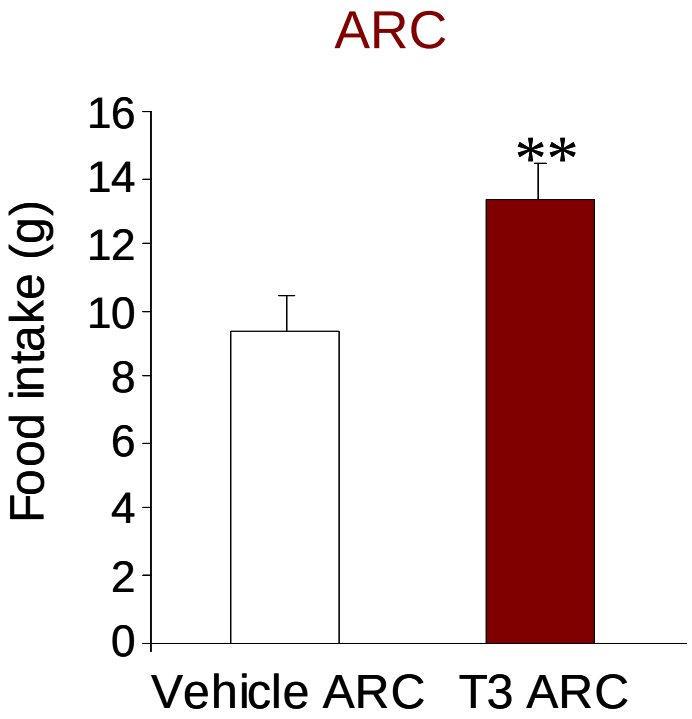
Varela L *et al* (2012). J Pathol 227:209-222

Woods *et al* (2008). Annu.Rev.Nutr. 28: 295-311

Martínez de Morentin PB *et al* (2013). Current Mol Med (in press)

T3 in the ARC induces food intake

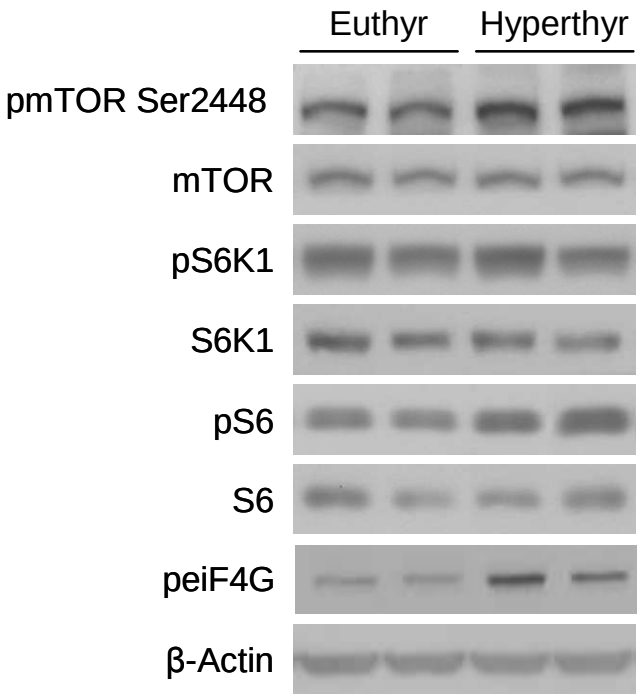


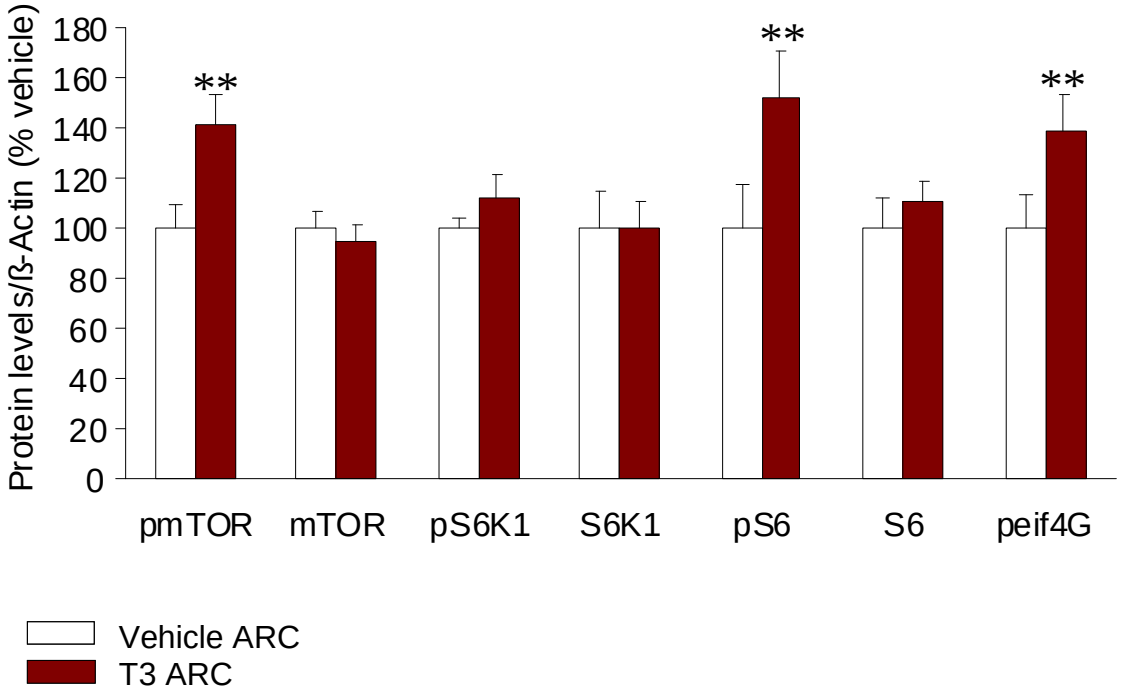


Varela L *et al* (2012). J Pathol 227:209-222

López M *et al* (2010). Nat Med 16: 1001-1008

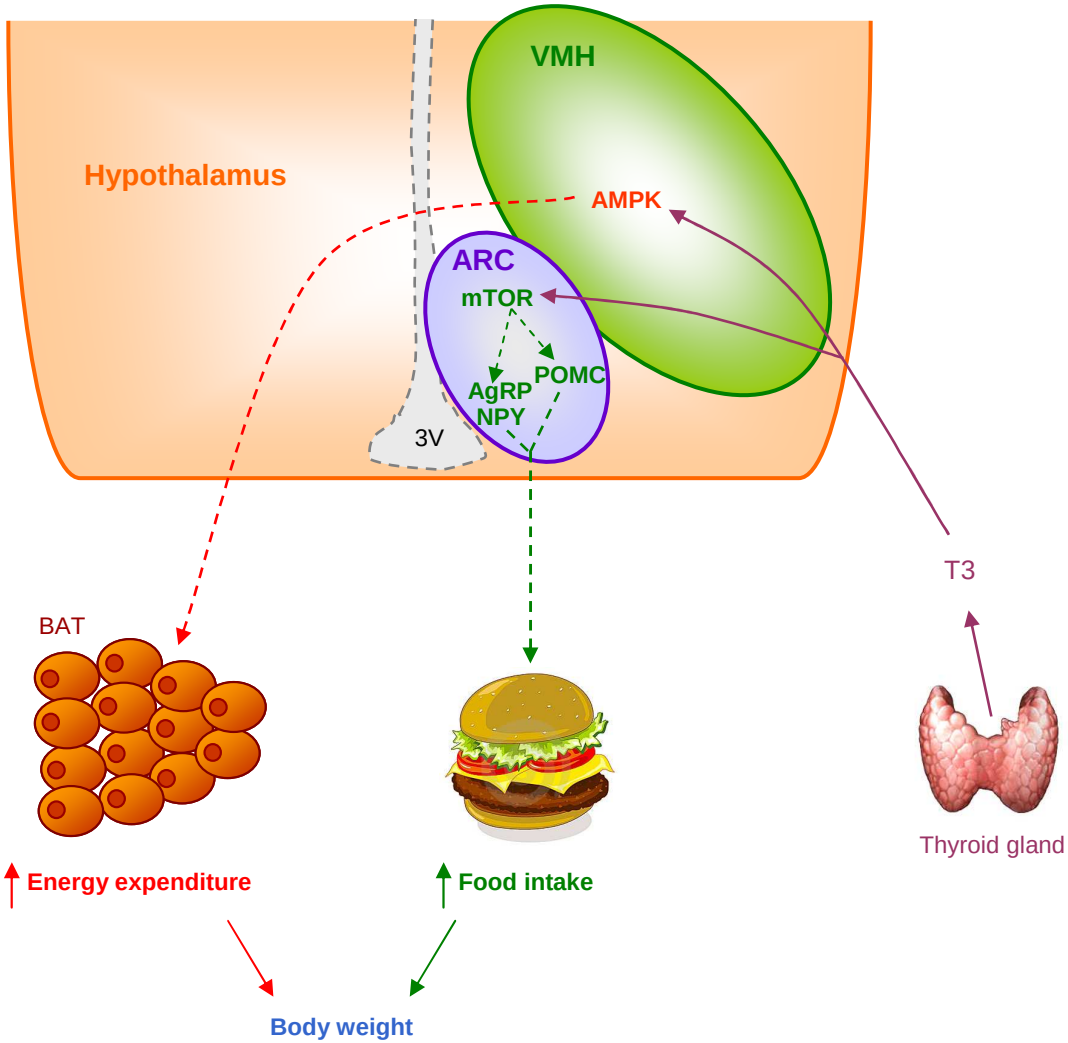
T3 in the ARC induces mTOR signalling





Varela L *et al* (2012). J Pathol 227:209-222

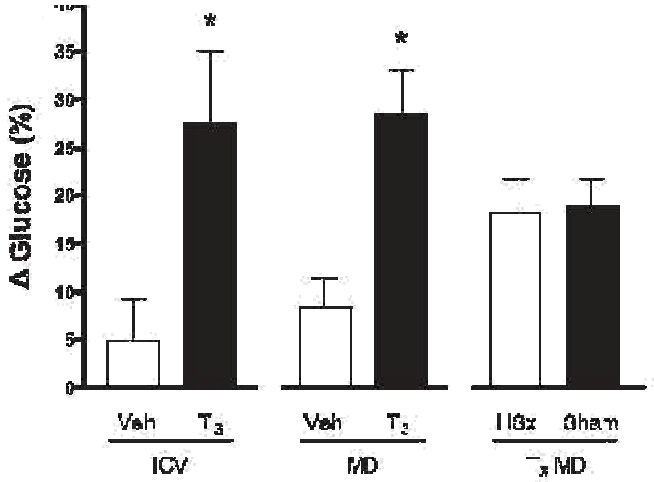
New central view of thyroid hormones actions on energy balance

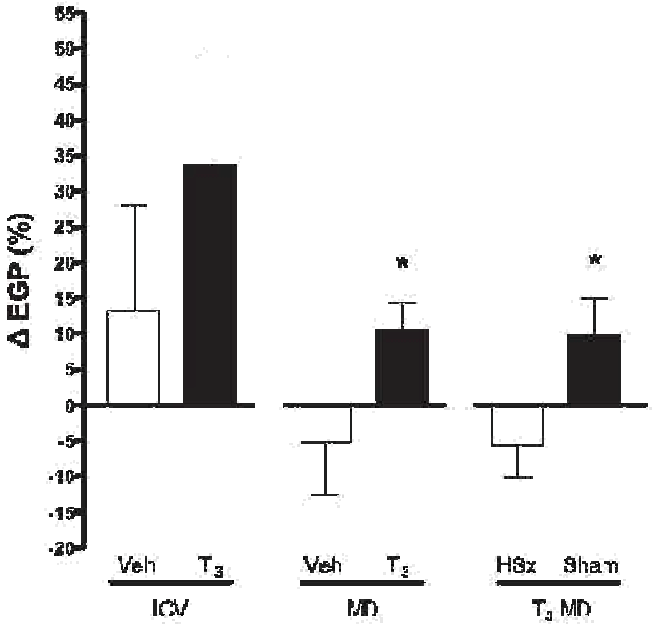


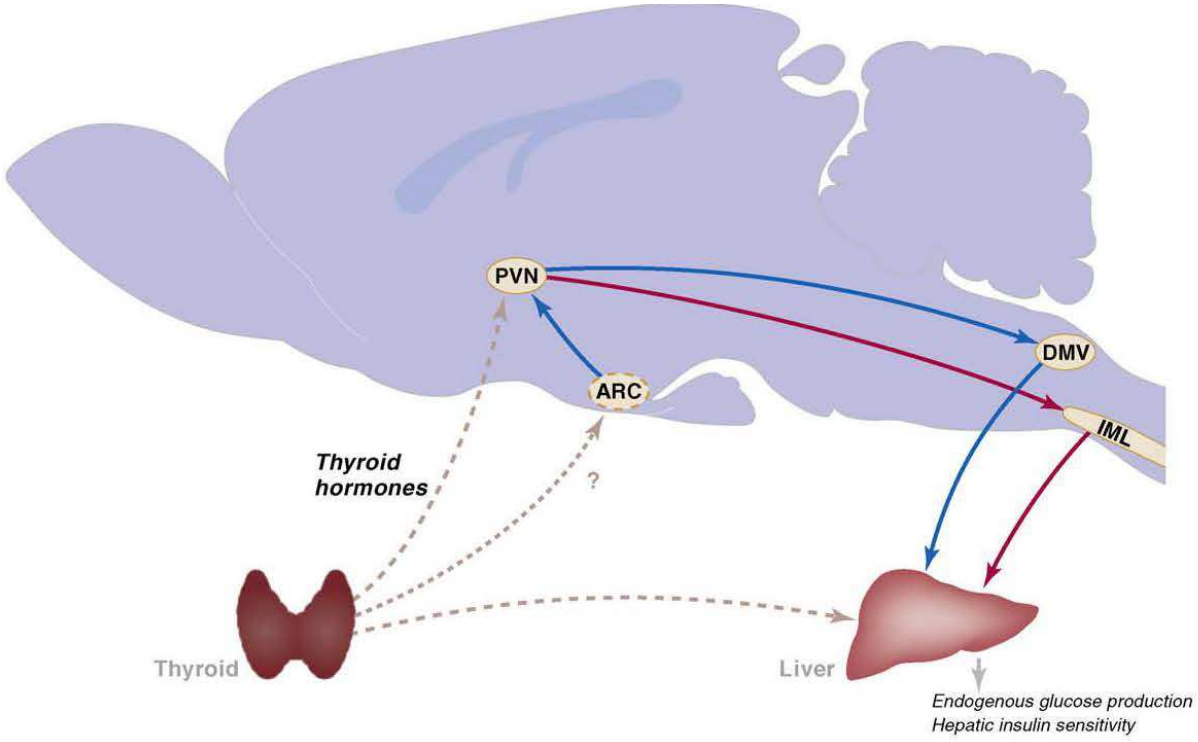
Varela L *et al* (2012). J Pathol 227:209-222

Central thyroid hormones and glucose homeostasis

T3 in the PVH induces hepatic glucose production through SNS







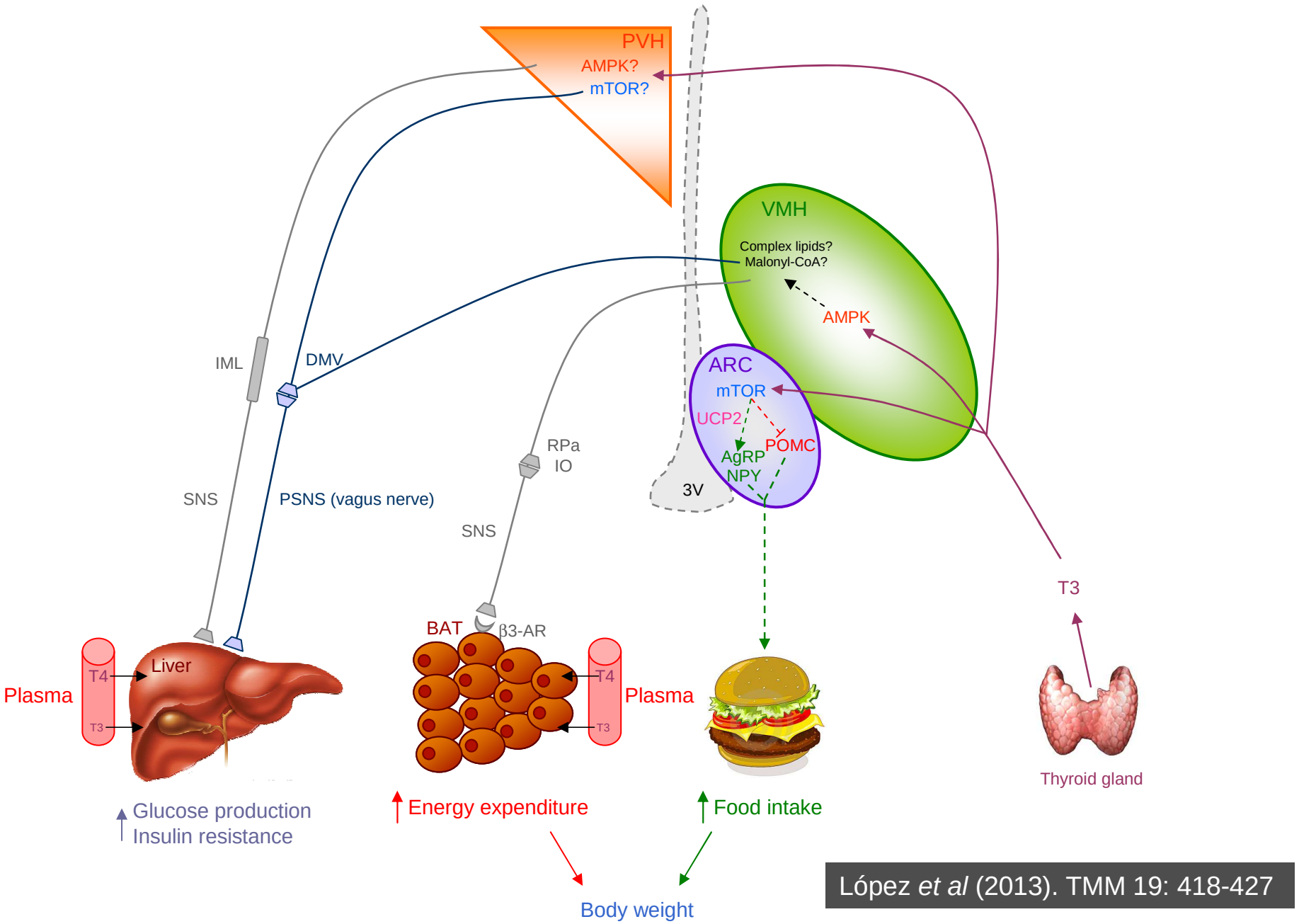
(effect independent of plasma T3, insulin, glucagon and CORT)

Klieverik LP *et al* (2008). AJP-EM 295:E513-E520

Klieverik LP *et al* (2009). PNAS 106:5966-5971

Fliers E *et al* (2012). TEM 21:230-236

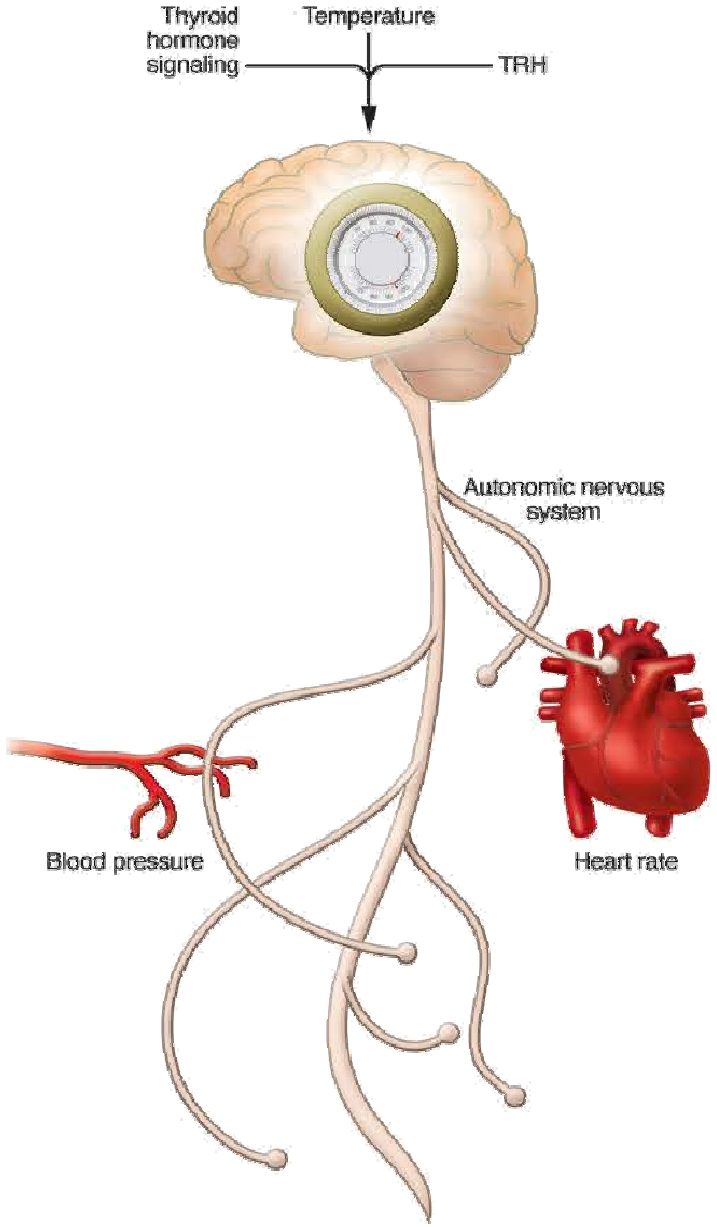
Energy balance regulation by thyroid hormones at central level

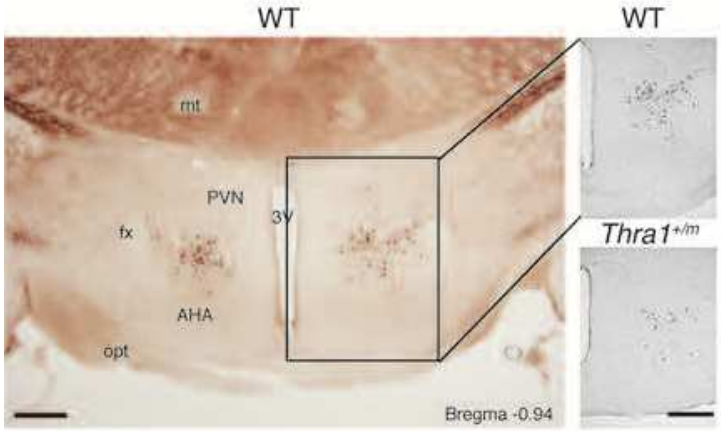


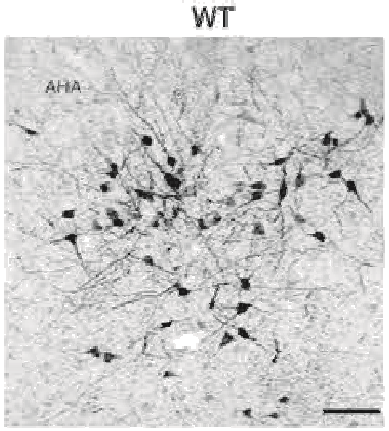
López *et al* (2013). TMM 19: 418-427

Central thyroid hormones and cardiovascular function

Central T3 modulates cardiovascular function







Mittag *et al* (2013). JCI 123: 509-516

Forrest & West (2013). JCI 123: 117-120

Summary

“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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PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Miguel Lopez)

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