Beth Israel Deaconess Medical Center

A teaching hospital of Harvard Medical School

American Thyroid Association
Basic Science Review
September 2012-September 2013

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Division of Endocrinology, Diabetes and Metabolism
Beth Israel Deaconess Medical Center and
Harvard Medical School

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Anthony Hollenberg)

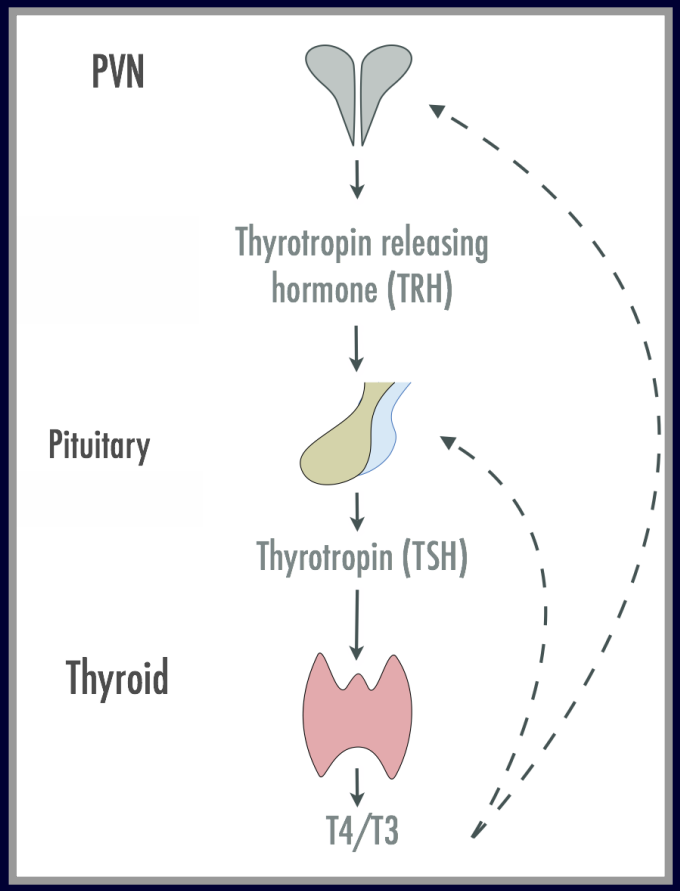
DISCLOSURES

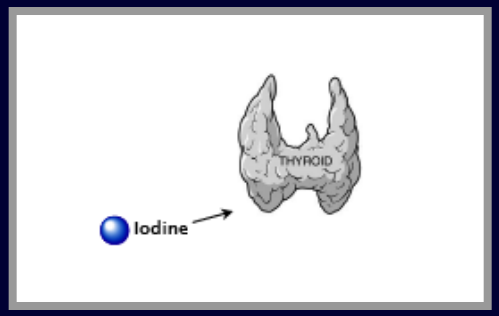
The commercial entities with which I/we have relationships do not produce health-care related products or services relevant to the content I am presenting.

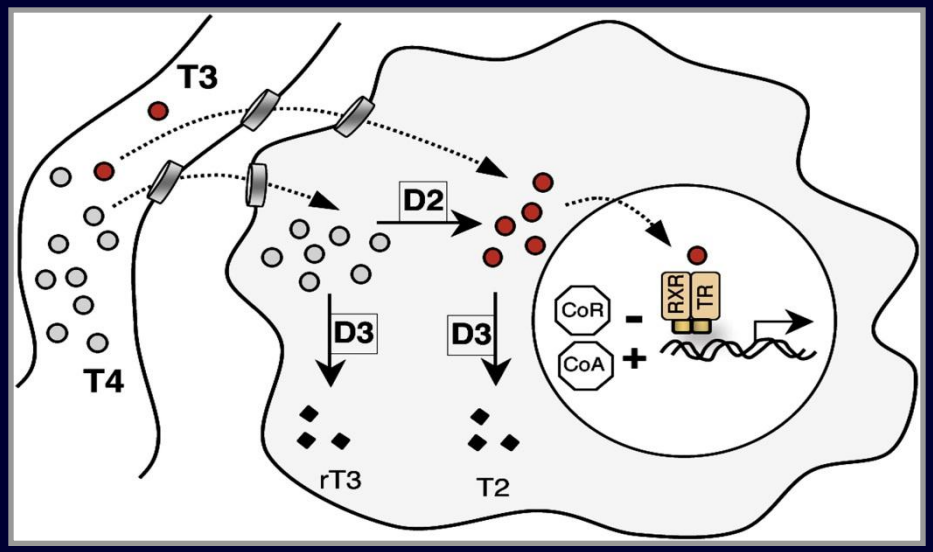
Methodology

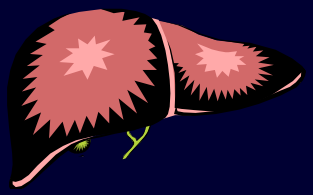
1. Review of Pub Med/Literature
2. Opinions of investigators in the field
3. Focus on discovery in thyroid hormone action and metabolism
4. Many other significant advances that could not be included.

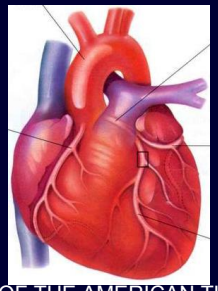
Thyroid Hormone Action

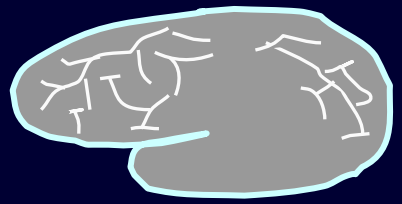


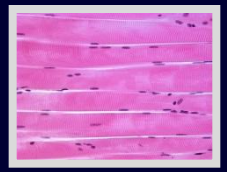


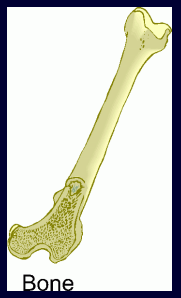




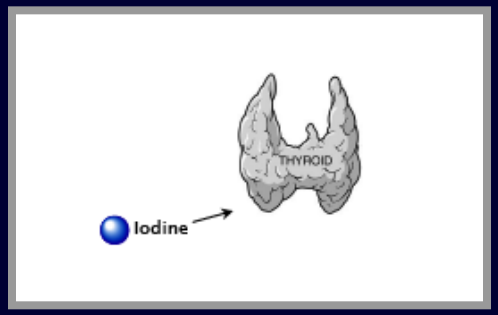




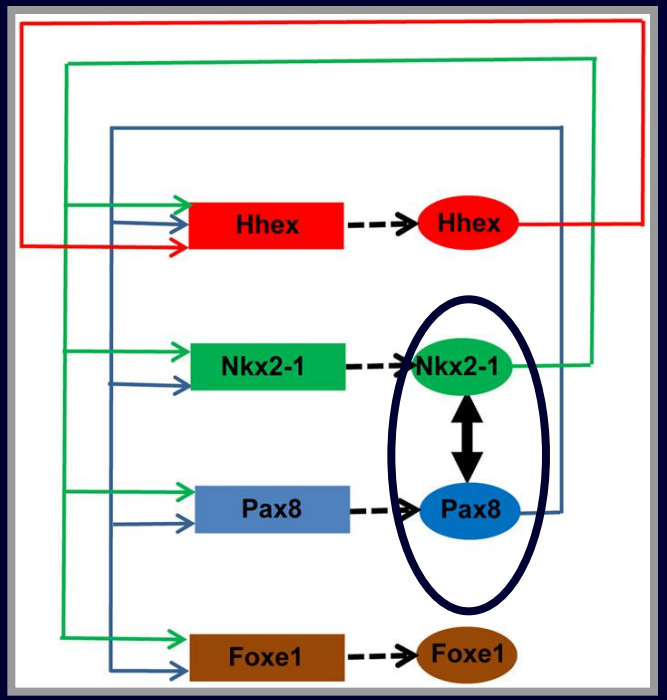




Thyroid Development

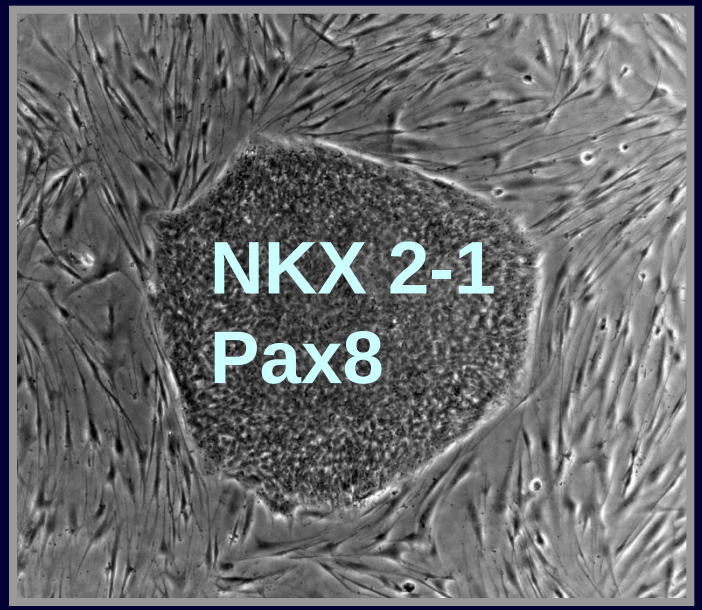


1/3000 congenital hypothyroidism



** De Felice and Di Lauro, Endocrinology, 2011*

Murine ESCs

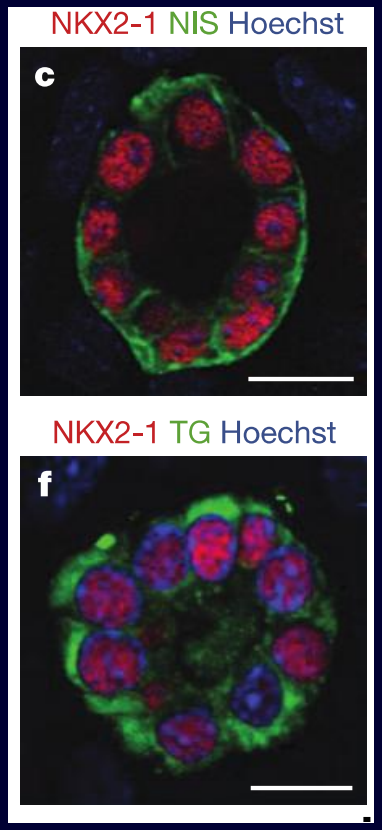


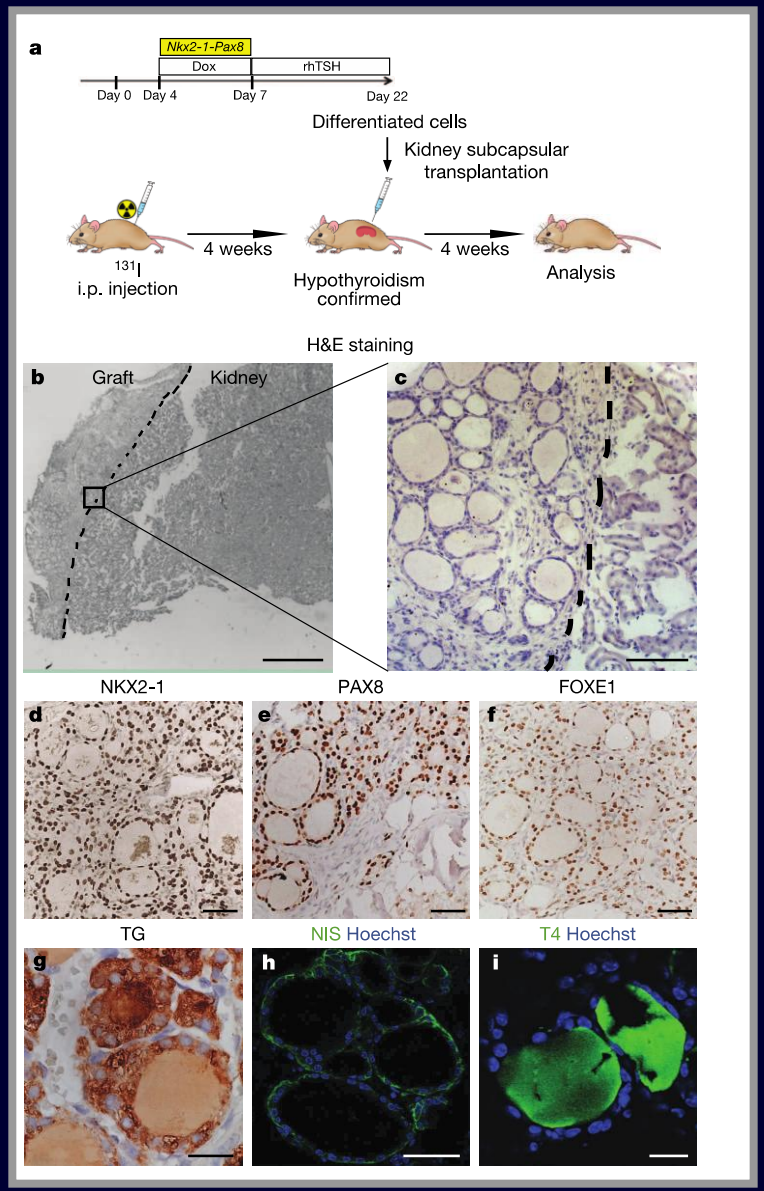
** Antonica et al, Nature, 2012*

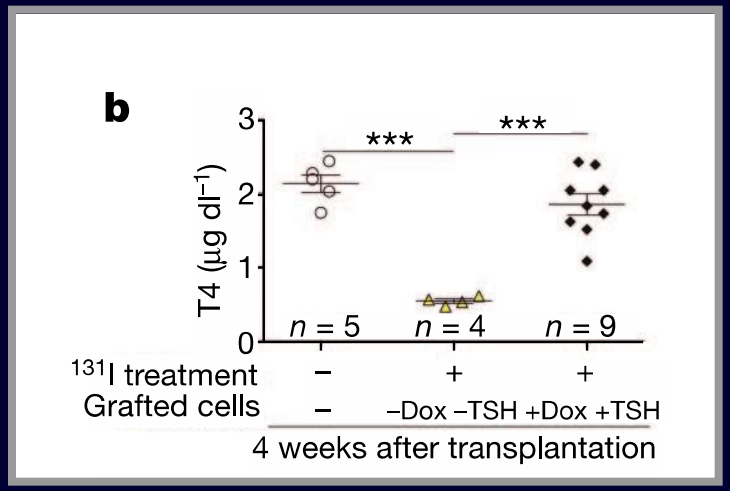
Thyroid Development

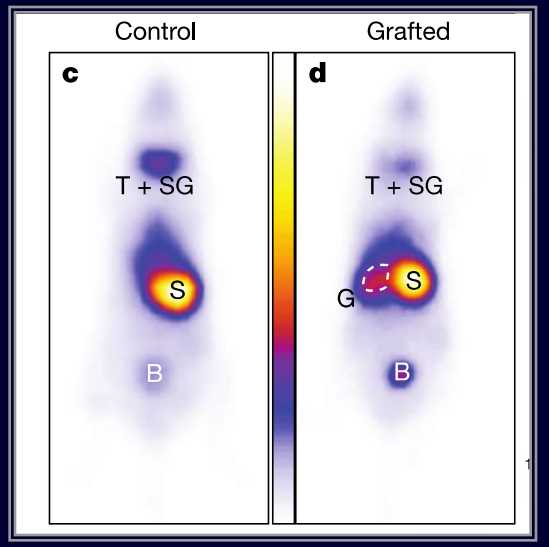
Antonica et al, Nature, 2012

ESCs



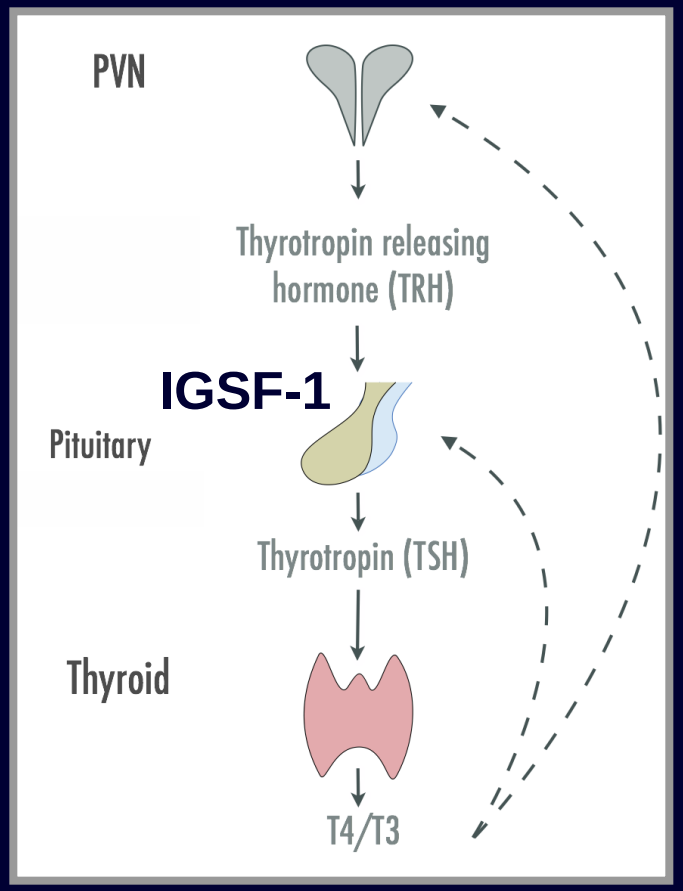


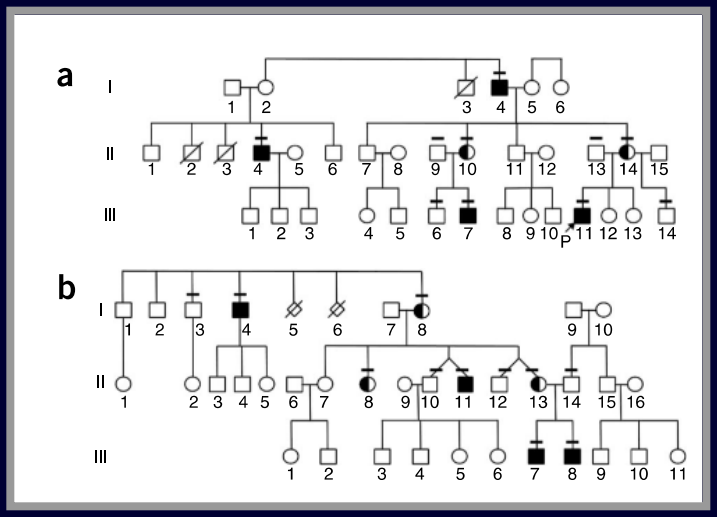




Thyroid Axis

Sun et al, Nature Genetics 2012



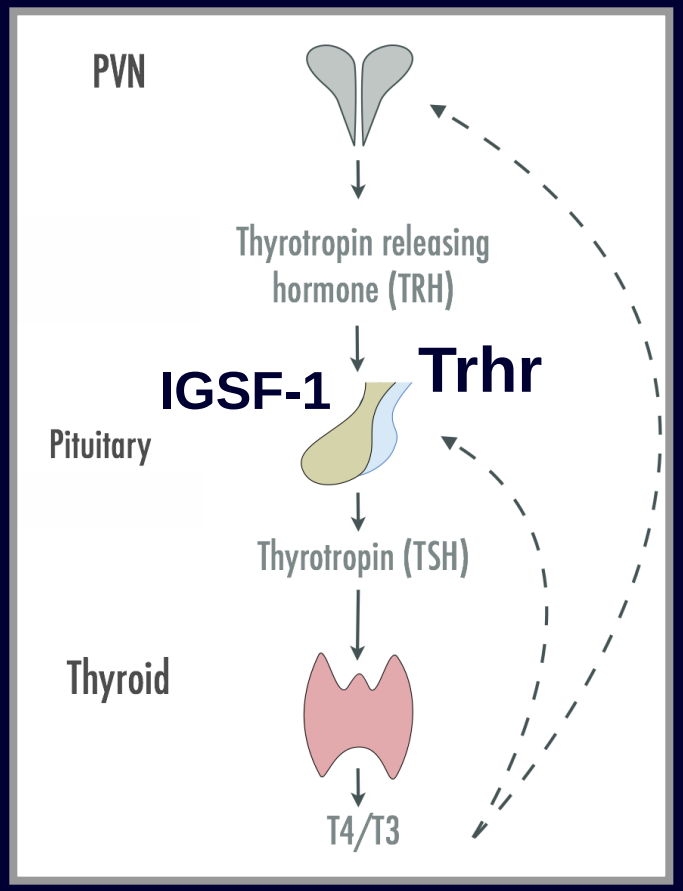


Index family w/congenital hypothyroidism, growth delay and testicular enlargement.

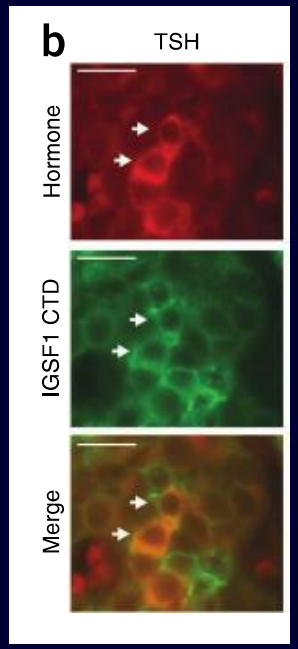
Mutation in IGSF-1 (immunoglobulin Superfamily -1)

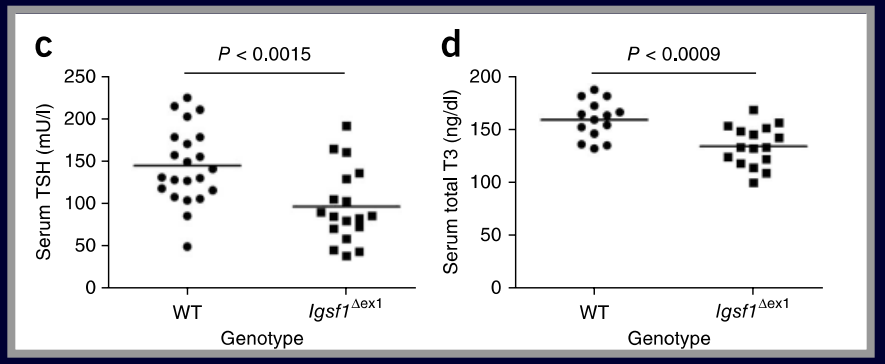
Thyroid Axis

Sun et al, Nature Genetics 2012

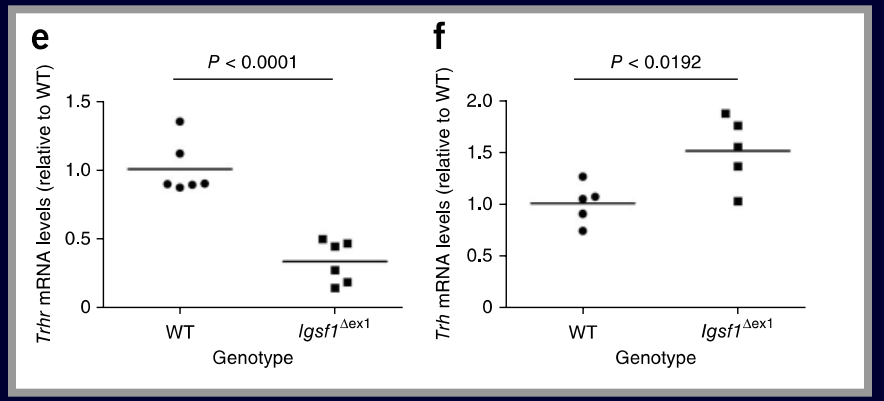


- Low TH levels and normal TSH
- Defective response to TRH





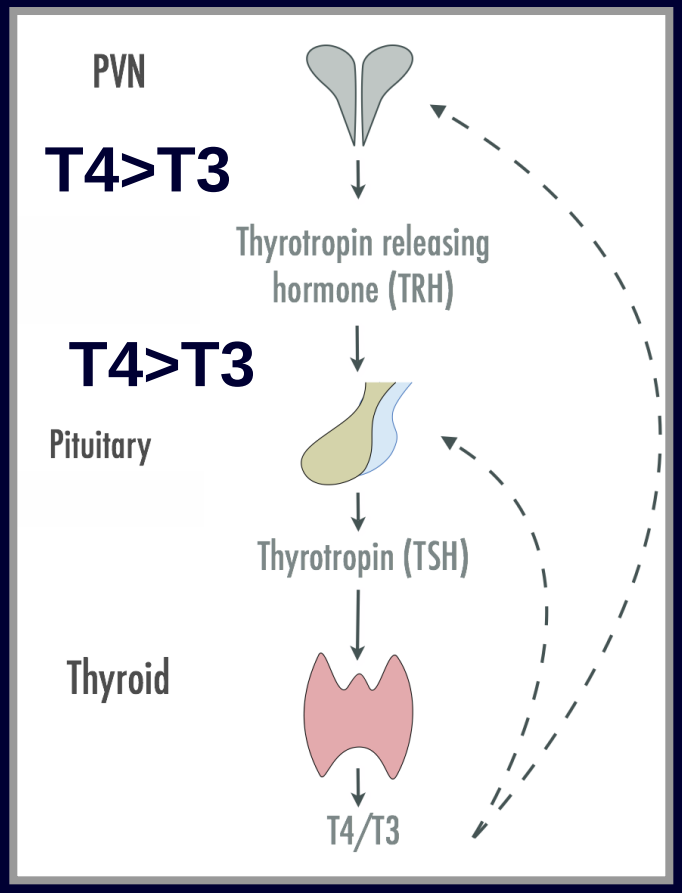
TSH T3

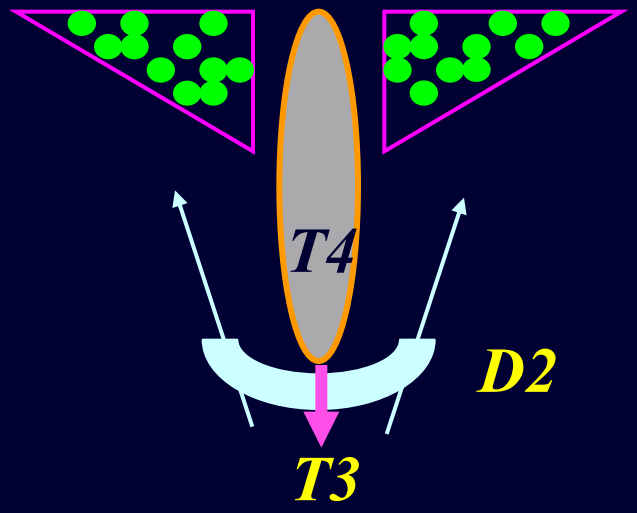


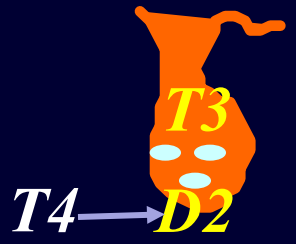
Trhr Trh

Thyroid Axis

Fonseca et al, J Clin Invest 2013







Astrocyte-Cre

loxp loxp

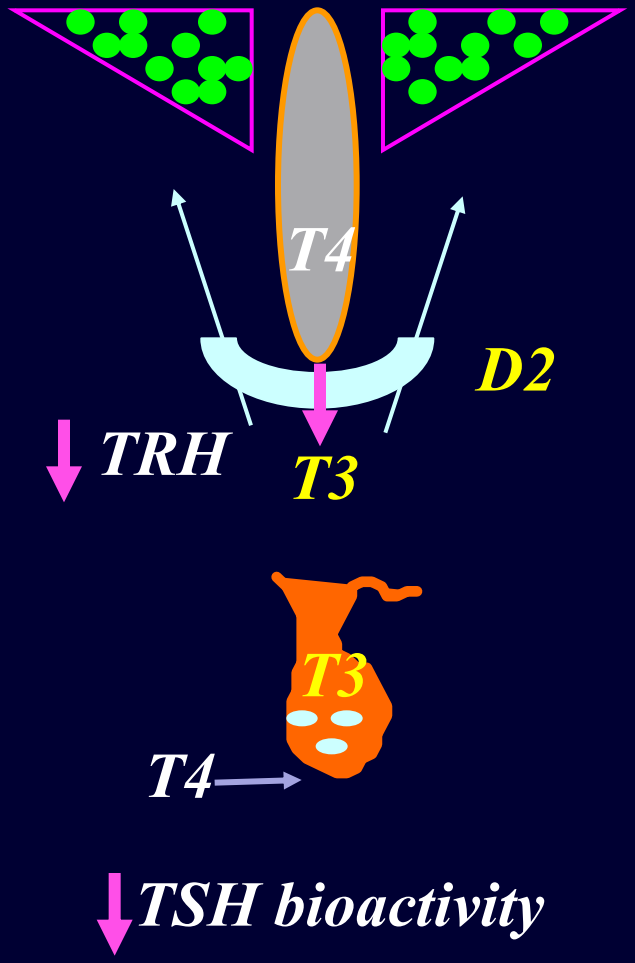
dio2

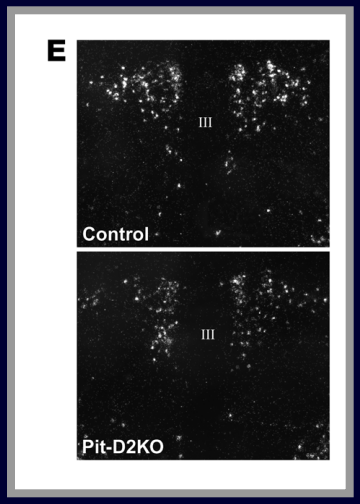
Pituitary-Cre

Type 2 deiodinase plays a critical role in central feedback but where?

Thyroid Axis

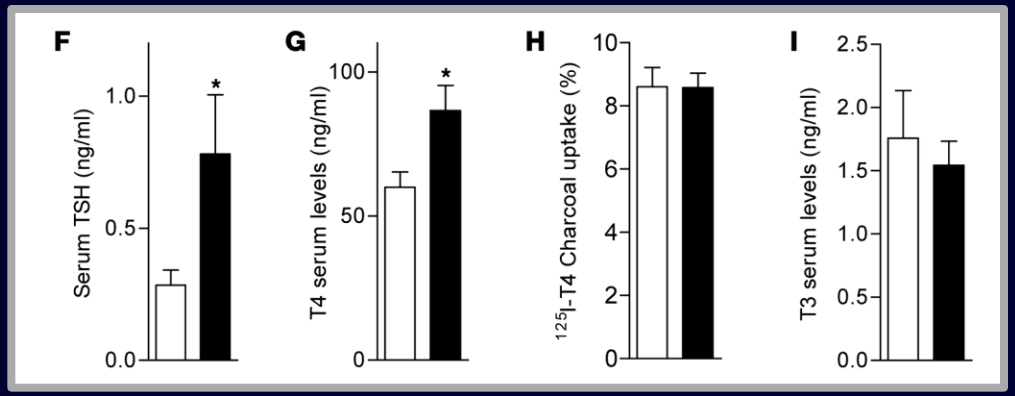
Fonseca et al, J Clin Invest 2013





1. Astrocyte KO – normal TFTs.

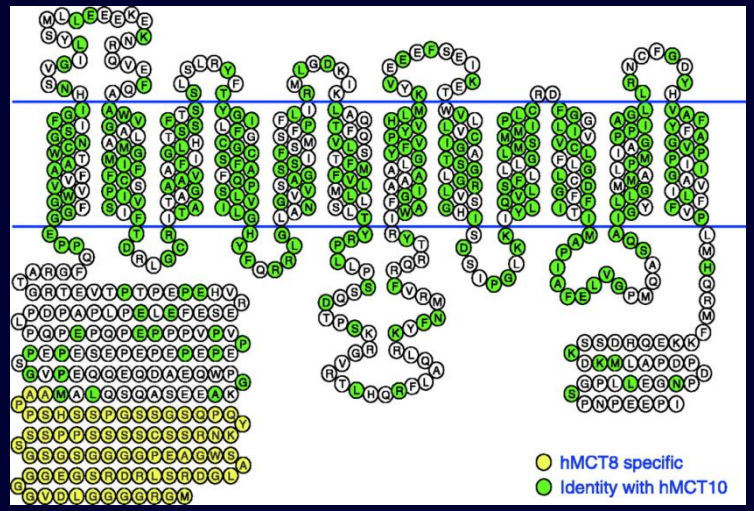
2. ? Phenotype of tanycyte KO.

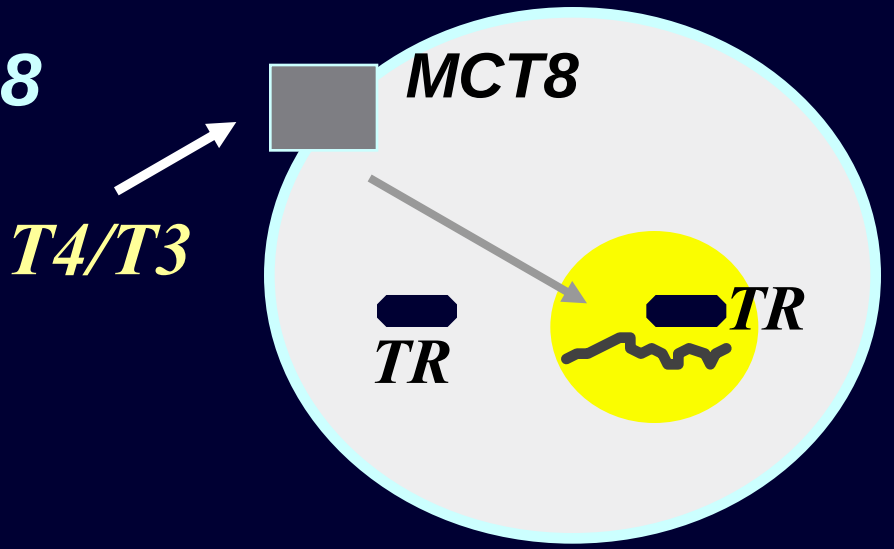


Reduction in TSH bioactivity preserves T3 levels

Cellular Actions of Thyroid Hormone

Monocarboxylate transporter 8





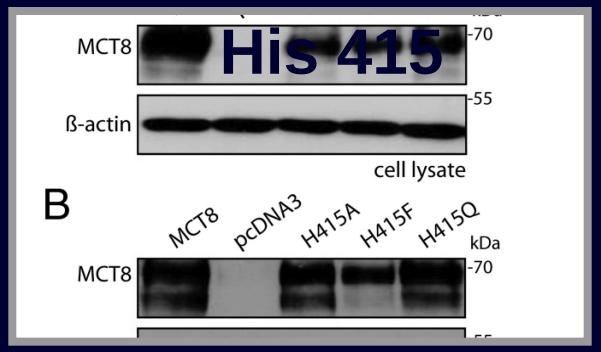
Defects in the MCT8 lead to AHD Syndrome. The tissue-specific effects of MCT8 lead to the TH abnormalities and the neurologic effects are likely mediated by the lack of MCT8 centrally.

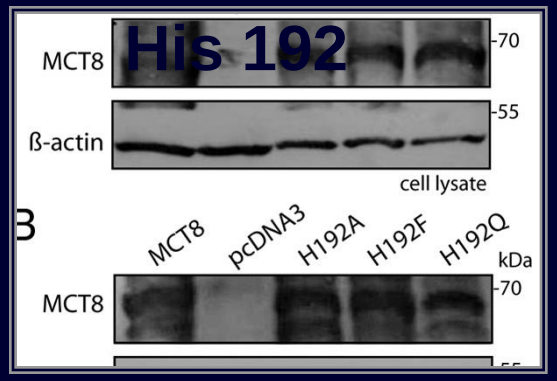
How does the MCt8 recognize TH? Can we bypass the MCT8?

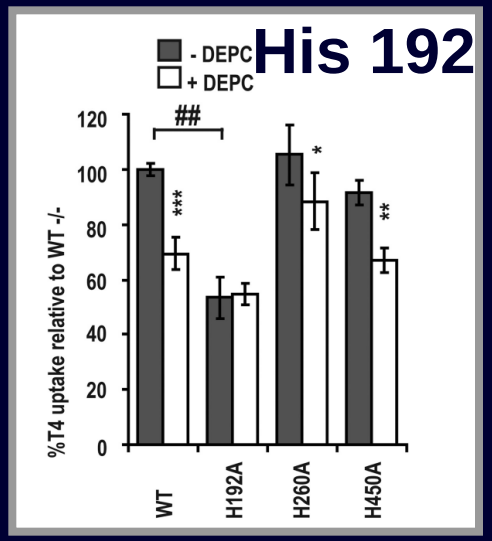
Cellular Actions of Thyroid Hormone

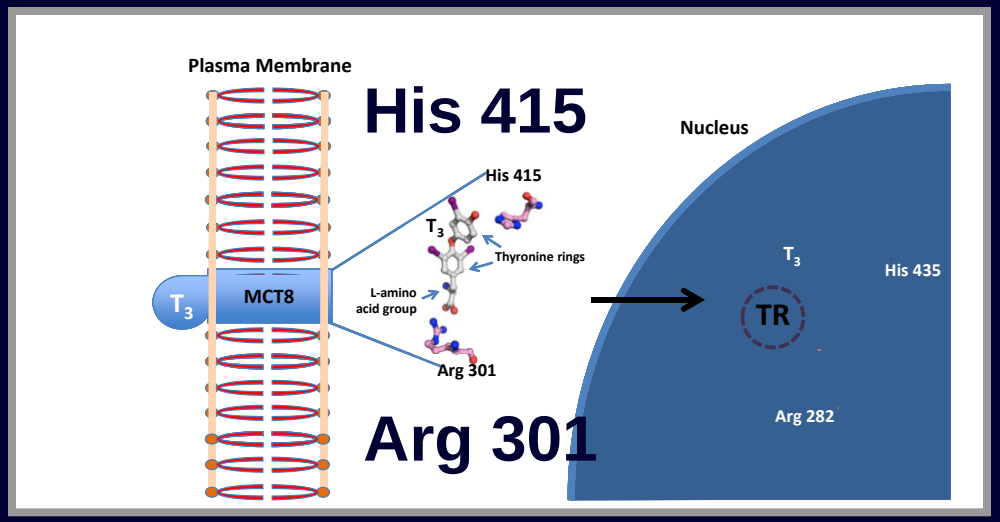
Groeneweg et al, Endocrinology 2013

Braun et al, Endocrinology 2013









Martagon et al, Endocrinology, 2013

1. His 192 identified by chemical inactivation.
2. Could it occlude the Channel?
3. Could it also effect a clamp?

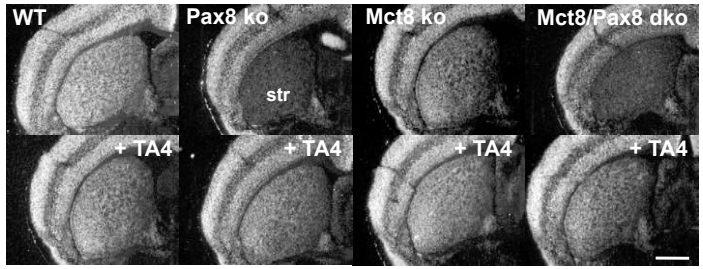
Cellular Actions of Thyroid Hormone

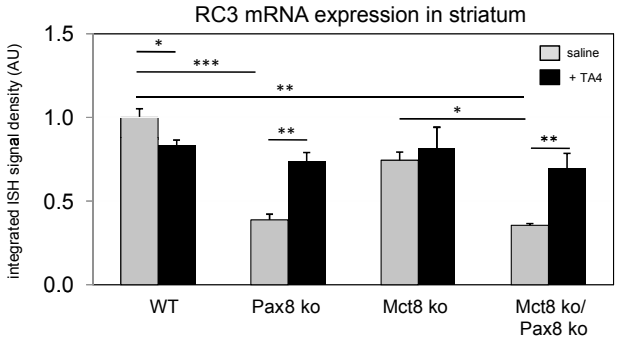
Verge et al, JCEM 2012

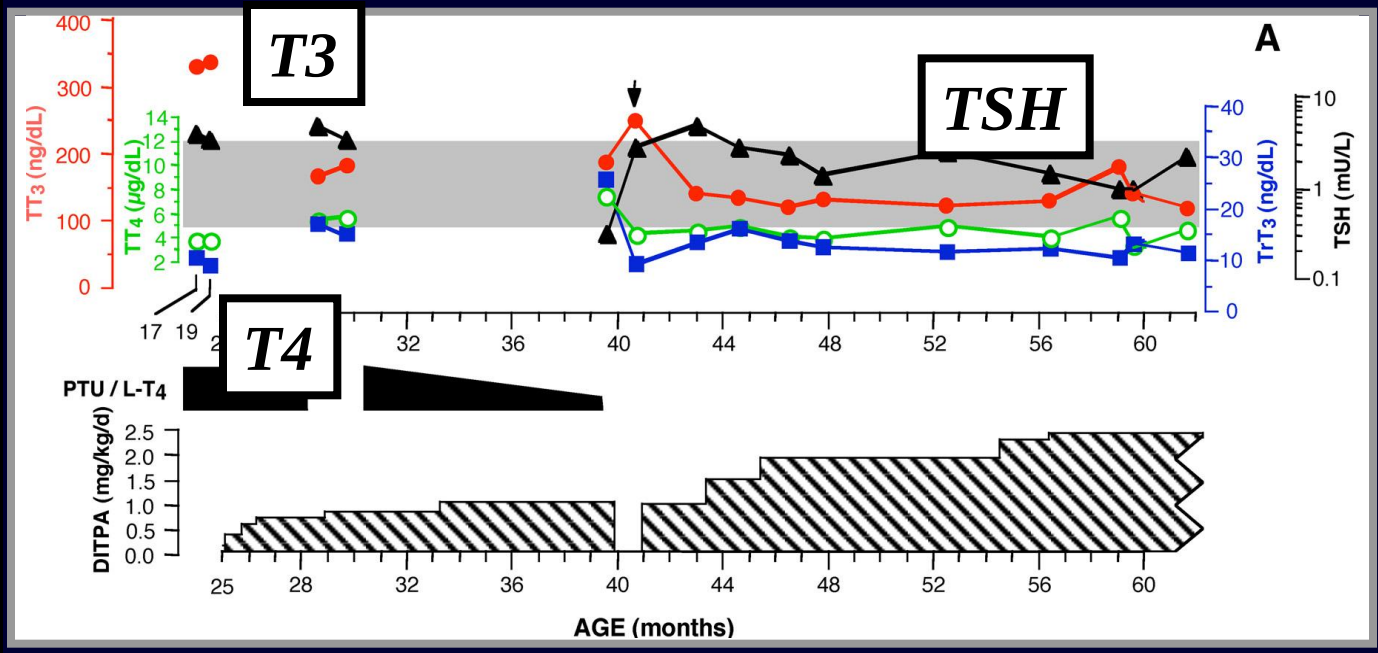
Horn et al, Endocrinology 2013

Can alternative ligands prevent AHDS??

WT Pax8 MCT8 DKO

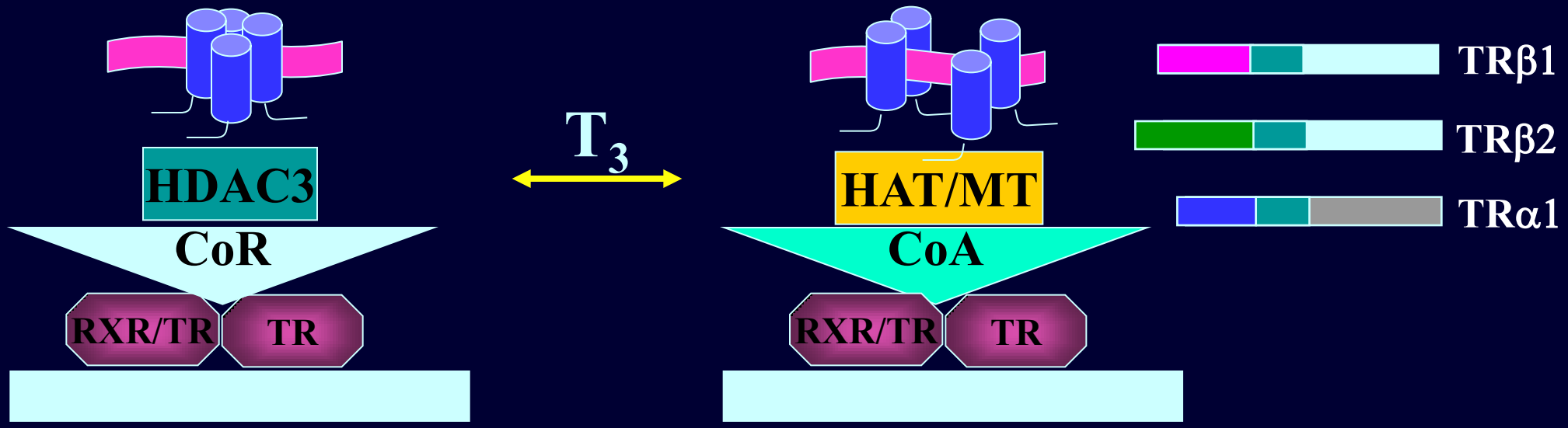




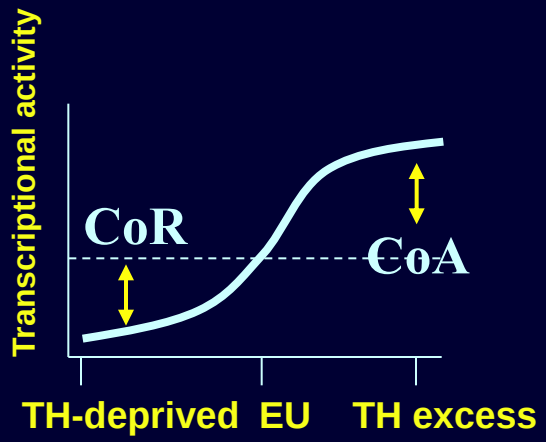


Fall in T3 allowed for weight gain; ?long-term safety

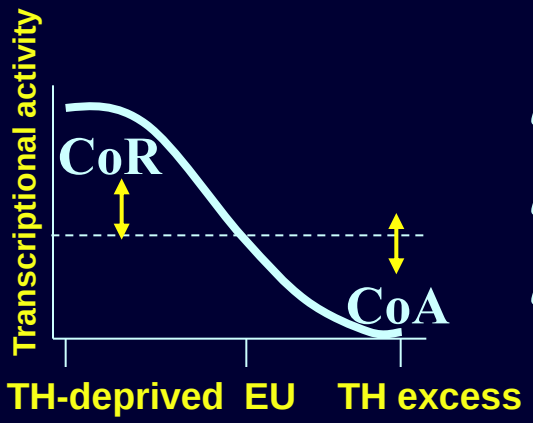
Cellular Actions of Thyroid Hormone



DR+4, PAL, Lys



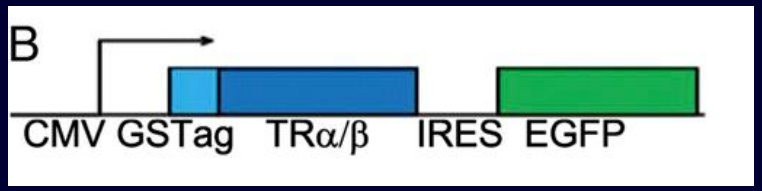
spot14
dio1
mod1



trh
tshα
tshβ

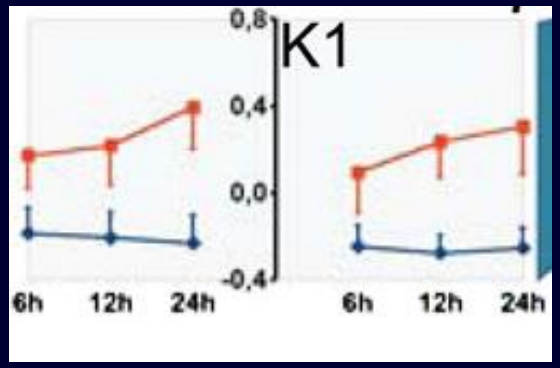
Cellular Actions of Thyroid Hormone

Chatonnet et al, Proc Natl Acad Sci 2013

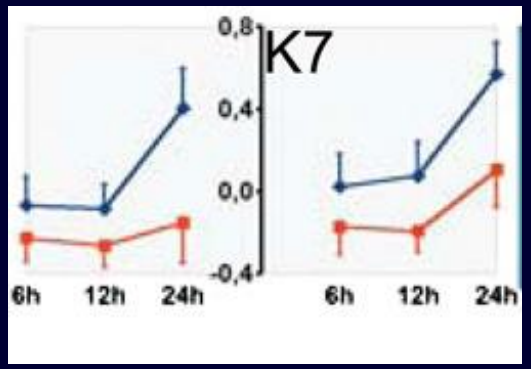


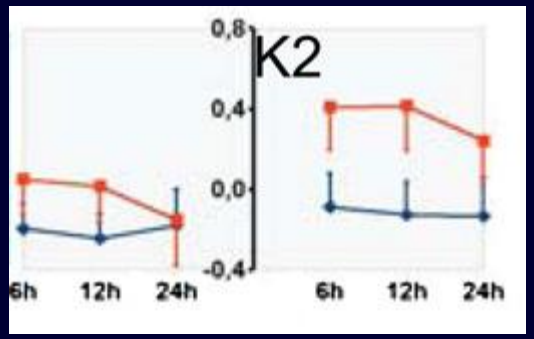
Murine cerebellar neurons

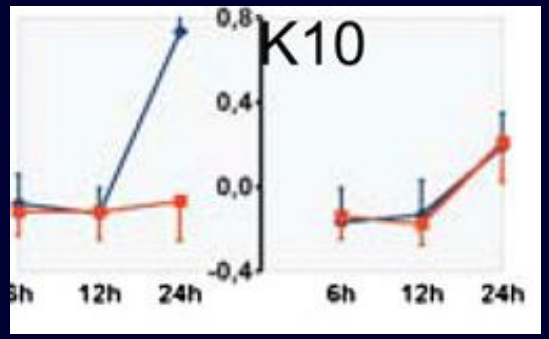
TRα1 TRβ1

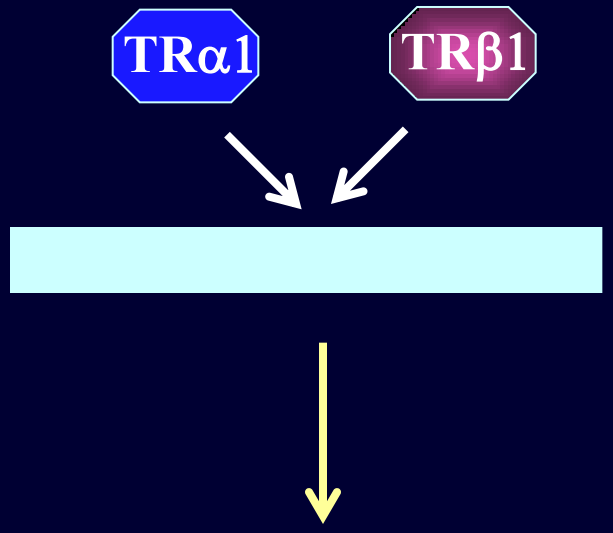


TRα1 TRβ1





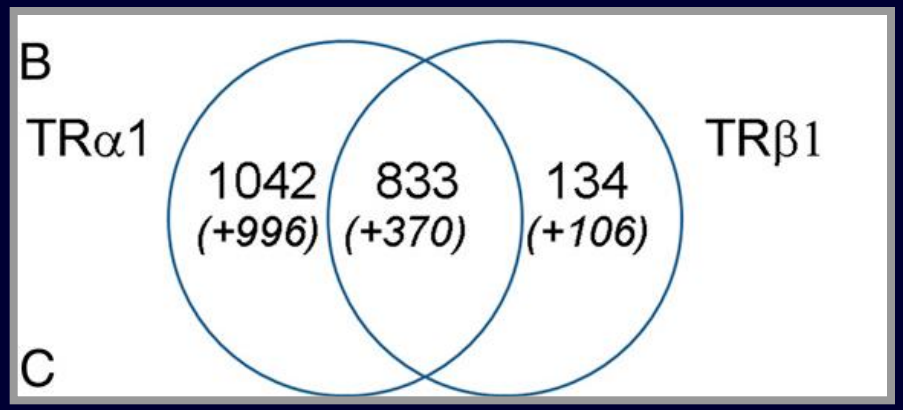


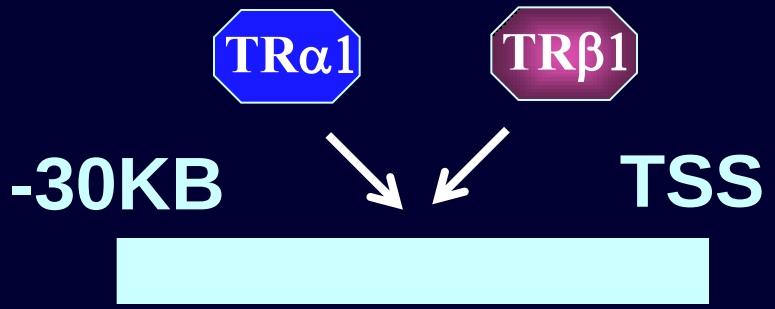


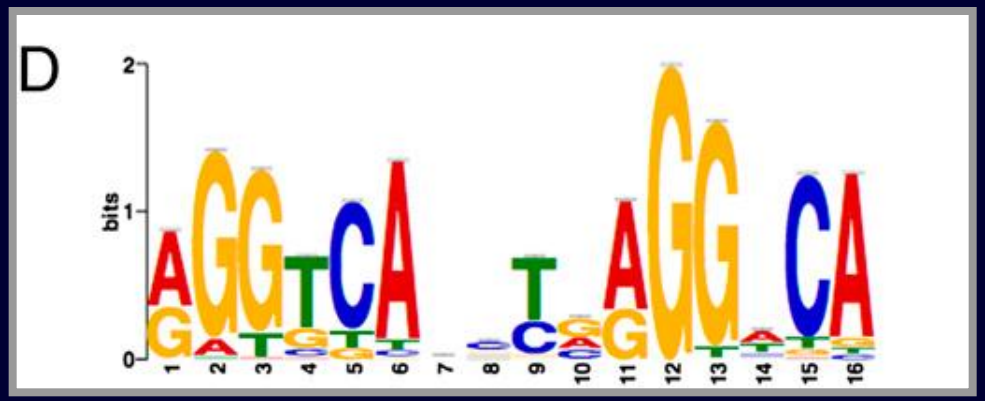
ChAP-Seq

Cellular Actions of Thyroid Hormone

Chatonnet et al, Proc Natl Acad Sci 2013





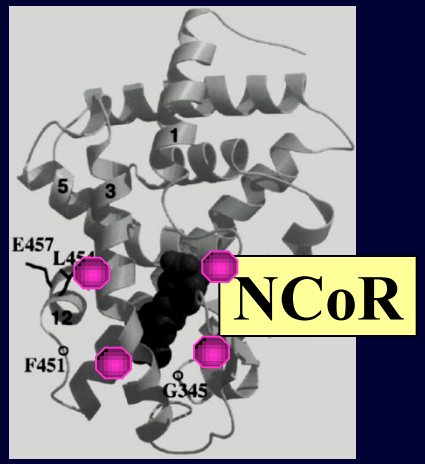


1. Positively regulated
2. Isotype-specific binding does not predict response
3. ? Negative TRE; ? Isoform Response.

Resistance to Thyroid Hormone

- Mutations found in the TRβ and TRα ligand-binding domain.

TRβ/α



Clinical Presentation-TRα resistance

1. normal TSH
2. low T4 and nl to high T3
3. growth delay
4. bradycardia

Mutations impair ligand-binding, and prevent:

1. CoRepressor release.
2. CoActivator recruitment

Cellular Actions of Thyroid Hormone

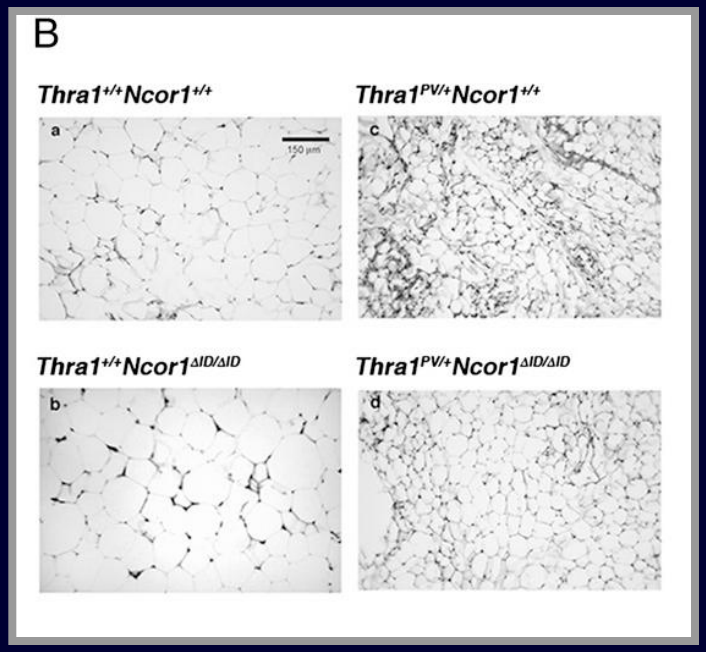
Fozzatti et al, Proc Natl Acad Sci 2013

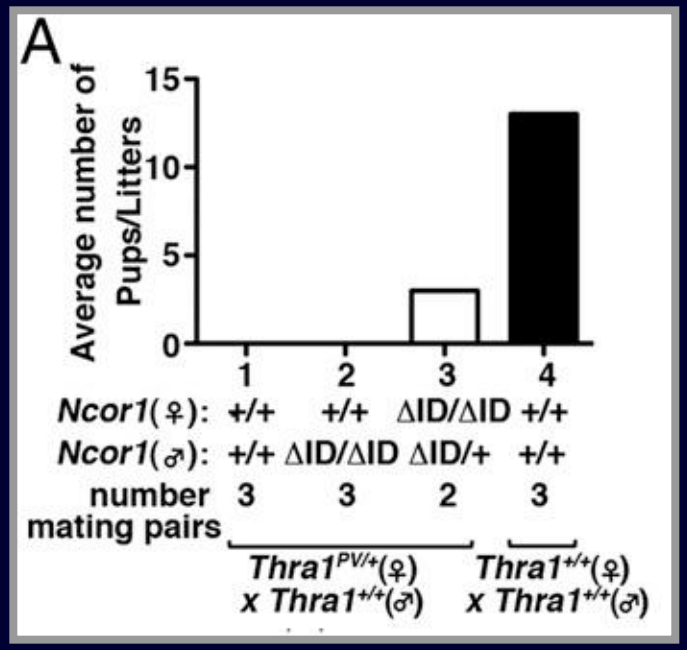
Mouse Models Recapitulate the Human Disease

$TR\alpha^{PV}$

NCoRΔID

1. No effect HPT axis
2. Improved growth (bone and weight)

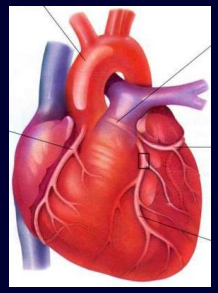




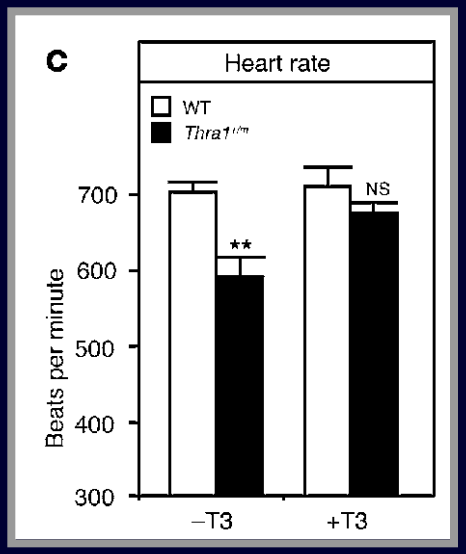
1. Role of SMRT?
2. Role of HDAC3?

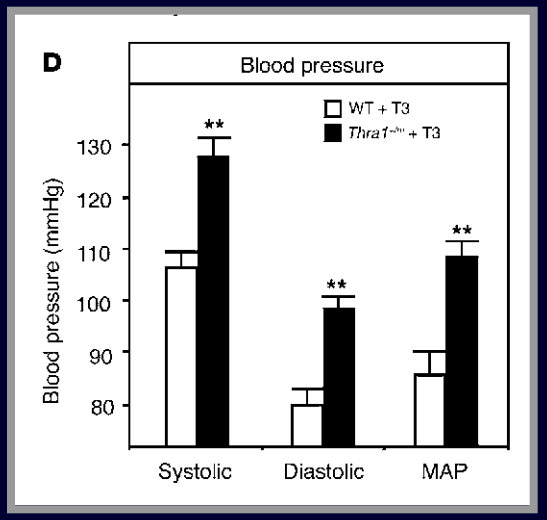
Peripheral Actions of Thyroid Hormone

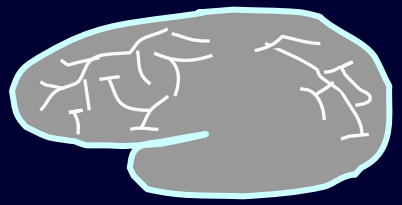
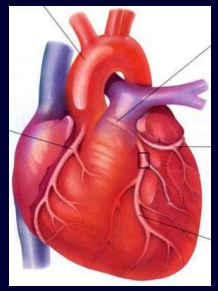
Mittag et al, J Clin Invest 2013

T_3 →  → Heart rate, blood pressure

$TR\alpha^{R384C}$



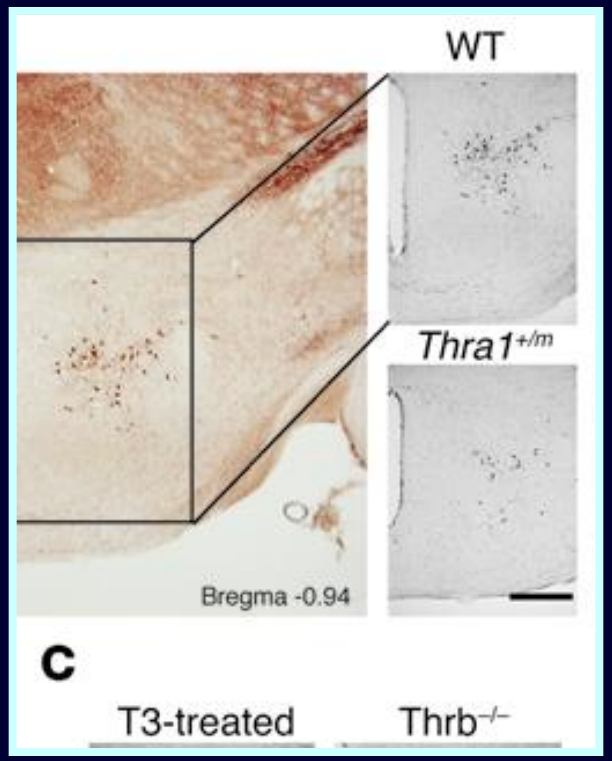


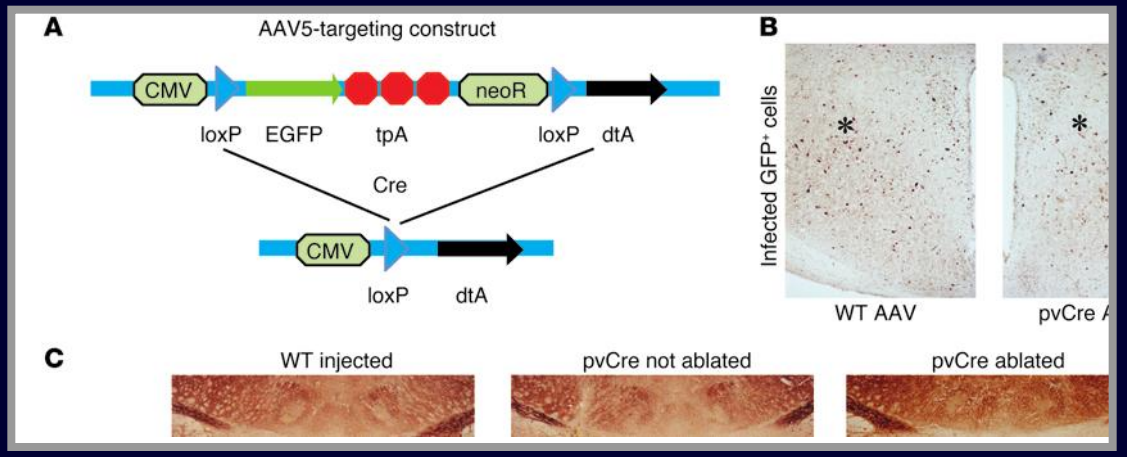
T_3 →  →  → Heart rate, blood pressure

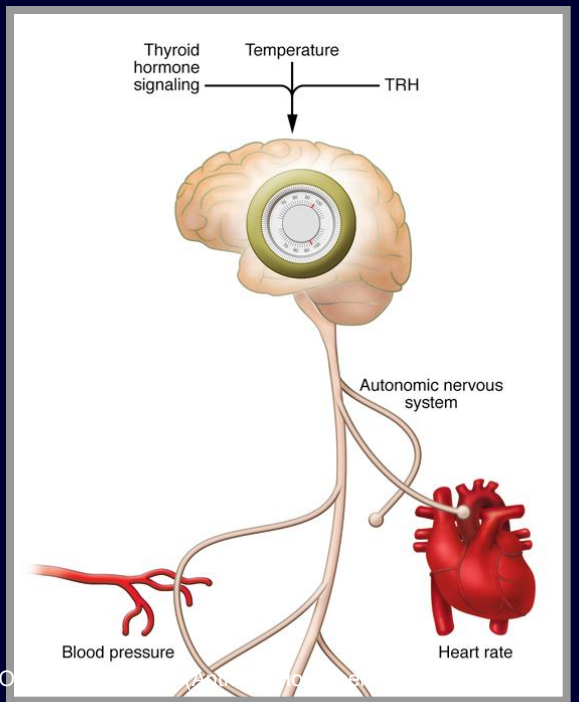
Peripheral Actions of Thyroid Hormone

Mittag et al, J Clin Invest 2013

AHA Parvalbumin

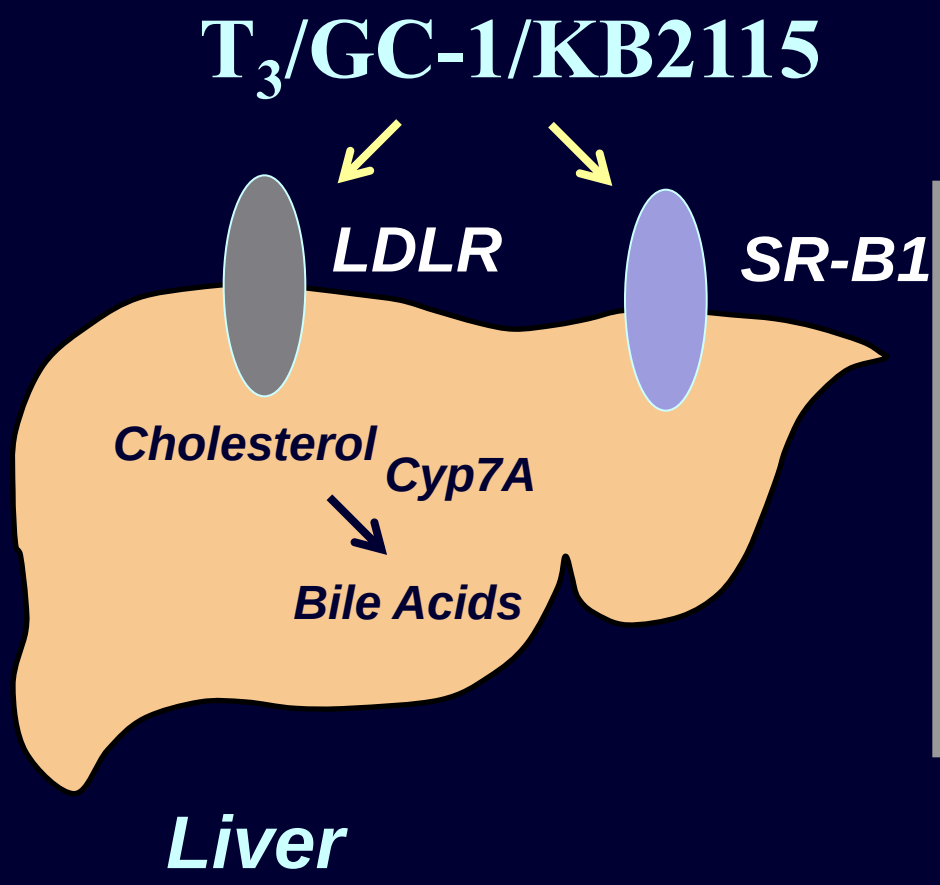


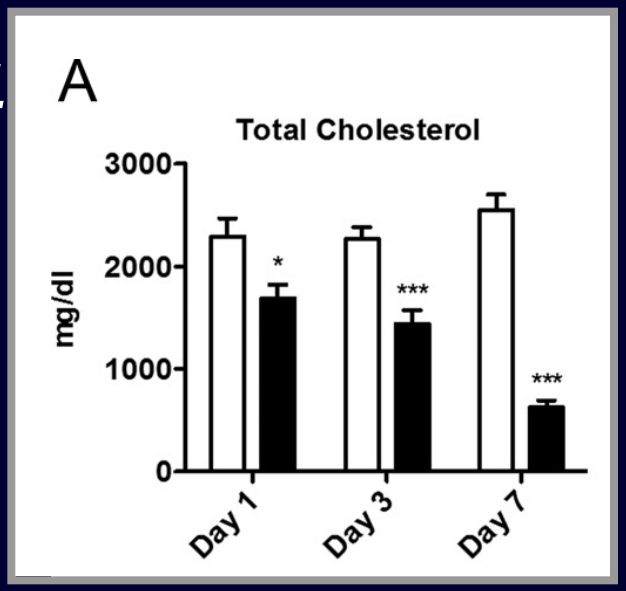


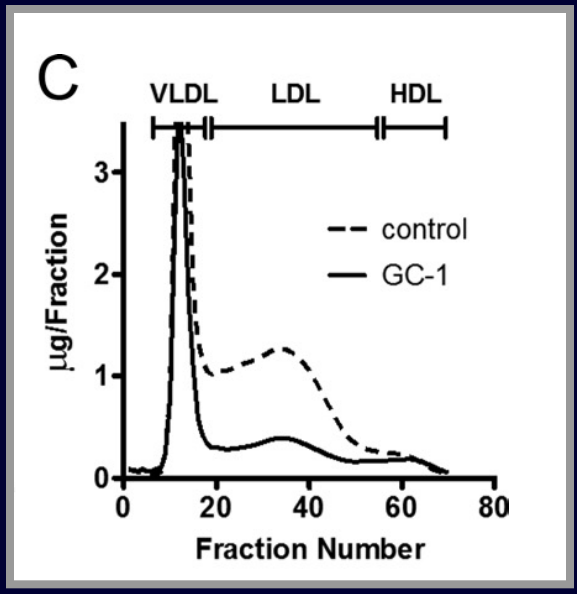


Peripheral Actions of Thyroid Hormone

Lin et al, Endocrinology 2012



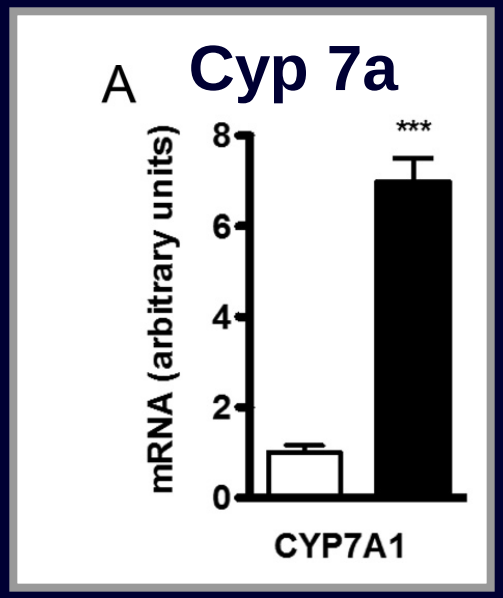


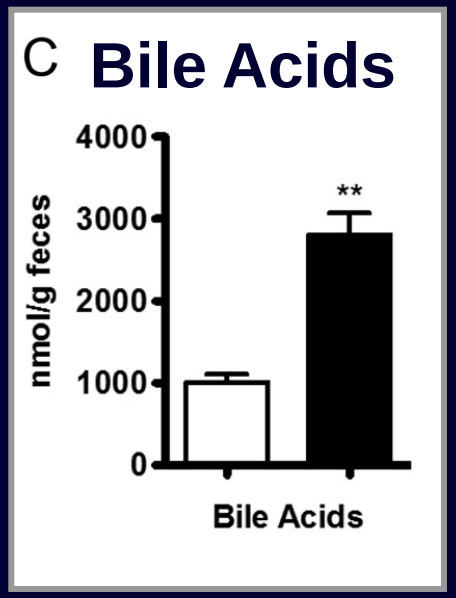


GC-1/LDL-R -/-

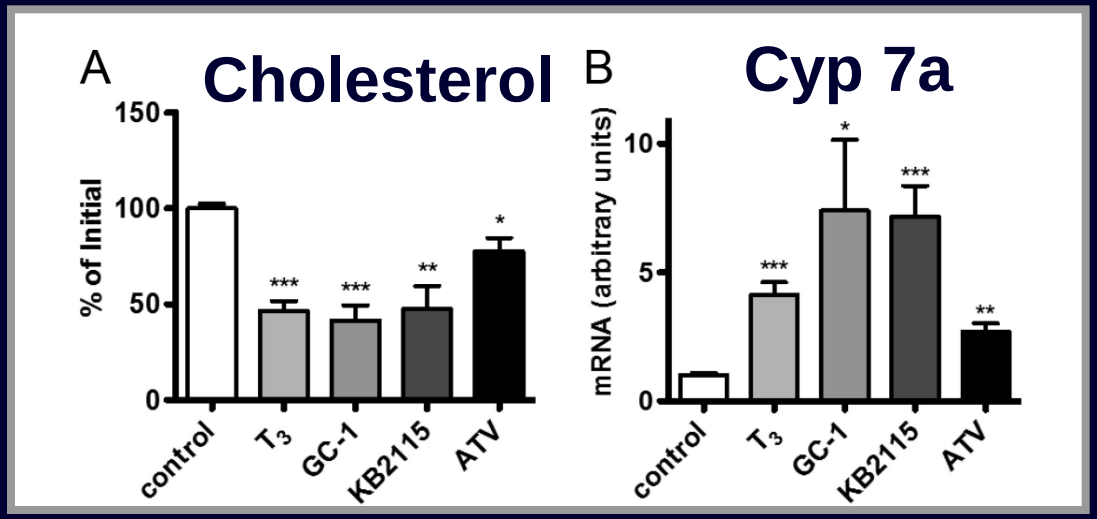
Peripheral Actions of Thyroid Hormone

Lin et al, Endocrinology 2012





T3, GC-1 > Statin

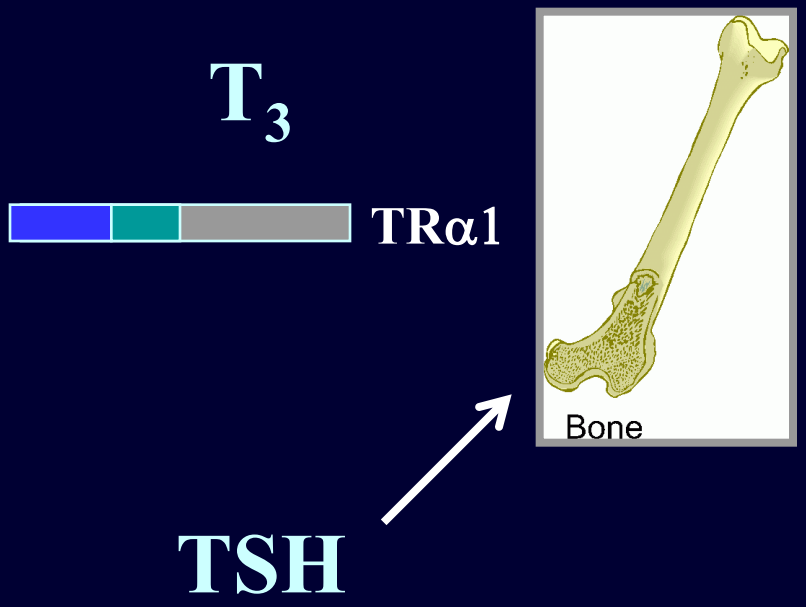


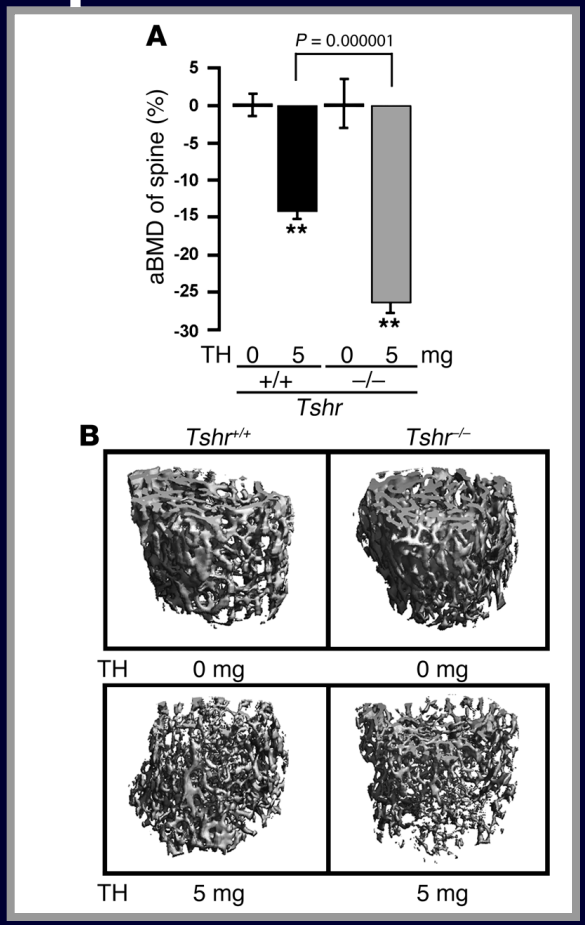
Peripheral Actions of Thyroid Hormone

Baliram et al, J Clin Invest 2013

Sun et al, Proc Natl Acad Sci 2013

TSHr absence accelerates osteoporosis

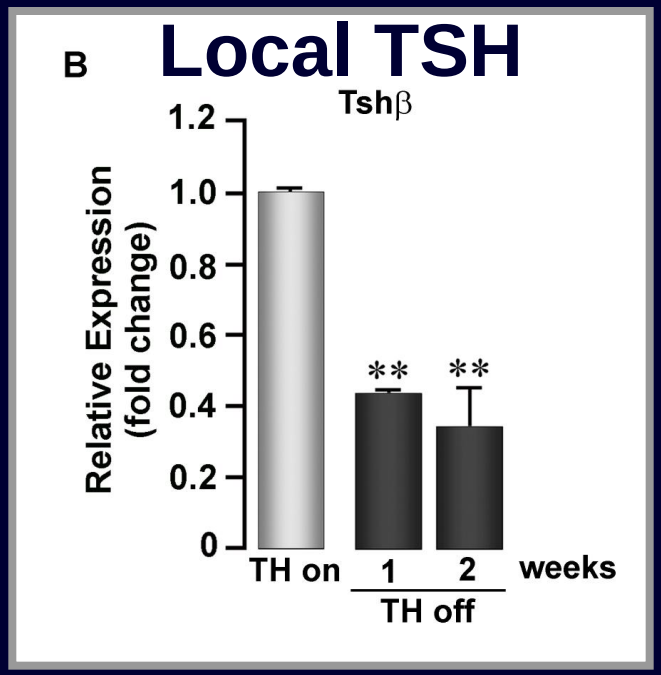




Peripheral Actions of Thyroid Hormone

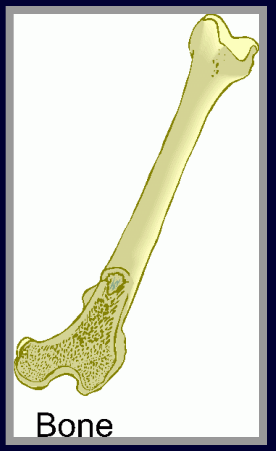
Baliram et al, J Clin Invest 2013

Sun et al, Proc Natl Acad Sci 2013



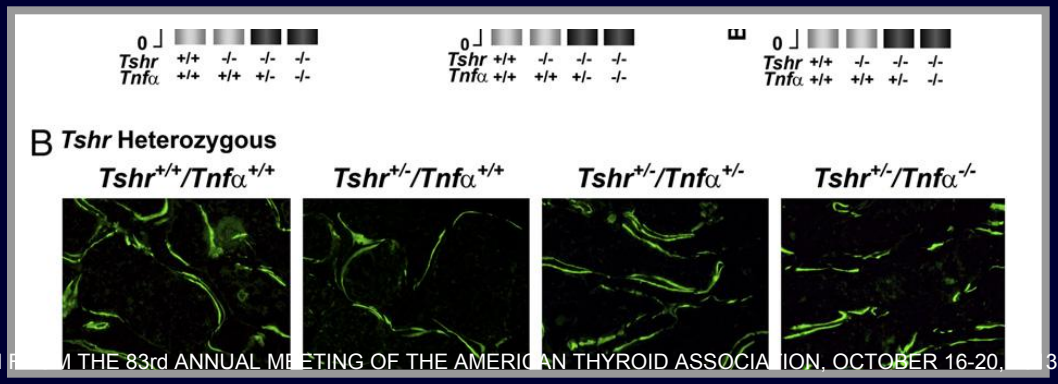
T_3

TRα1



TSH → TSHr → TNFα

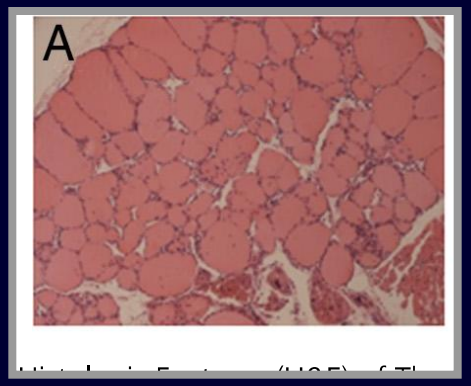
TNFα → RANKL

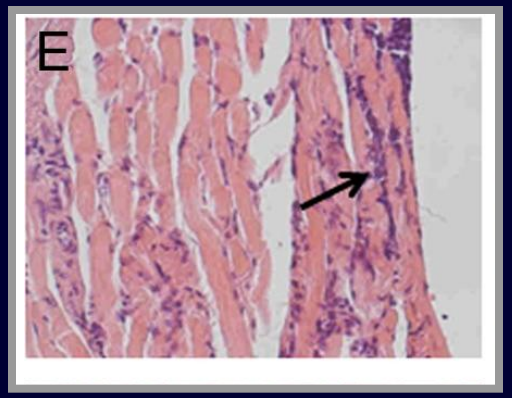


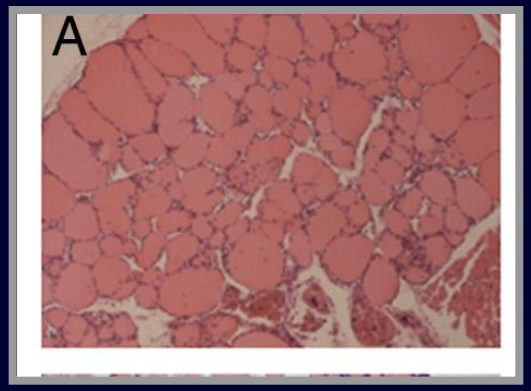
Graves' Opthalmopathy

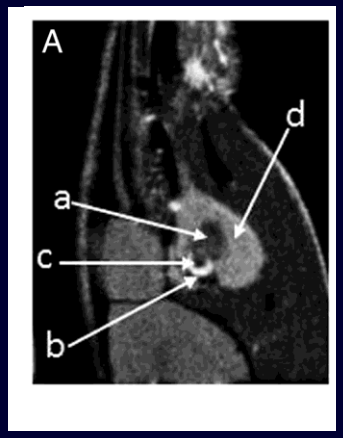
Moshkelgosha et al, Endocrinology 2013

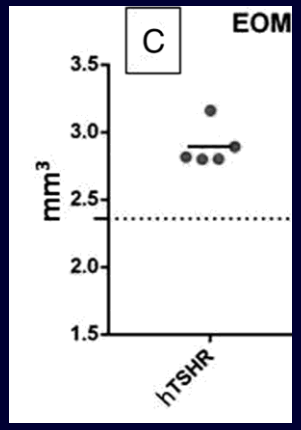
22 female mice immunized hTSHrA plasmid
Variable thyroid response but most hypothyroid









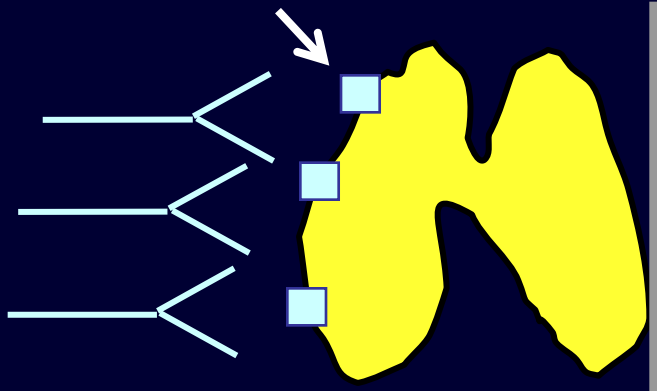


Mouse model of GO

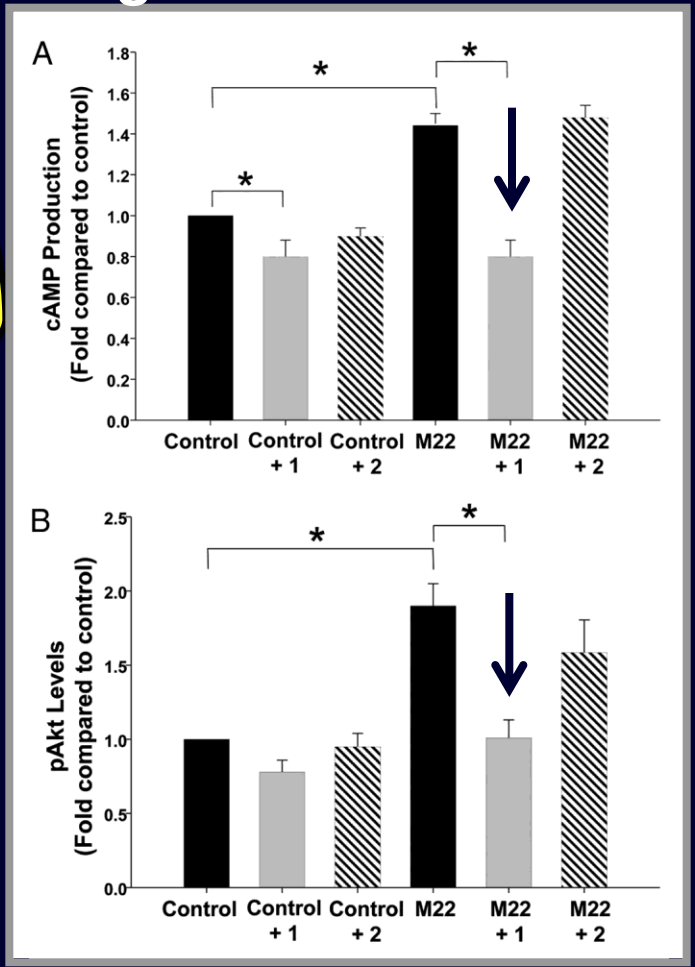
Graves' Opthalmopathy

Turcu et al, J Clin Endo Metab 2013

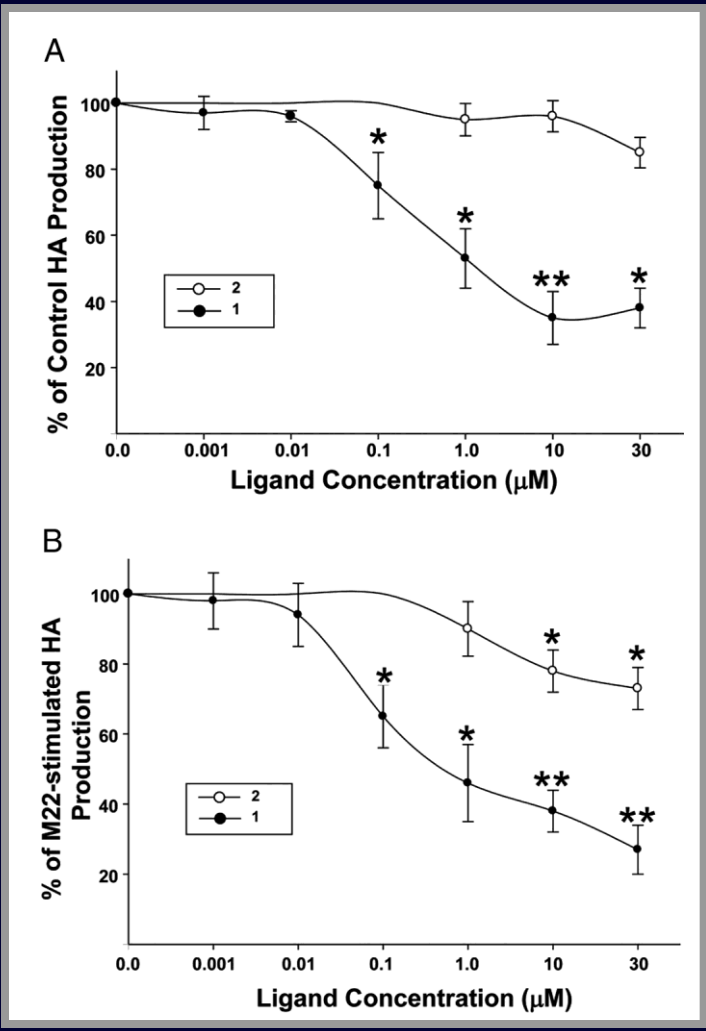
TSHrA1



TSHrA1Blocks M22 Signal Transduction



TSHrA1Blocks M22 induced Hyaluronan

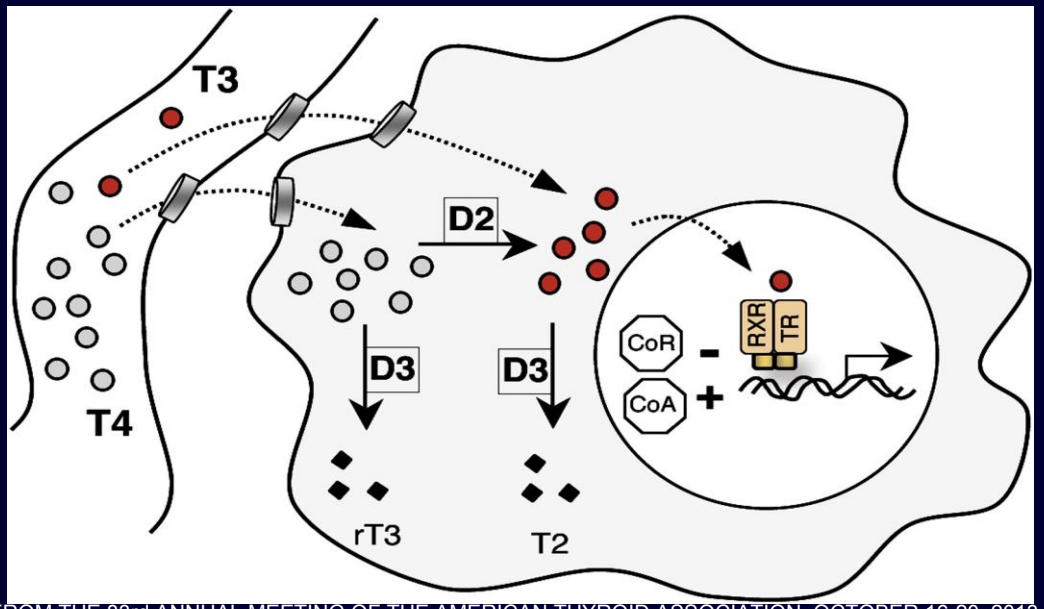


Conclusions

American Thyroid Association Guide to Investigating Thyroid Hormone Economy and Action in Rodent and Cell Models

Report of The ATA Taskforce on Approaches and Strategies to Investigate Thyroid Hormone Economy and Action

Antonio C. Bianco (chair)[1*], Grant Anderson[2], Douglas Forrest[3], Valerie Anne Galton[4], Balázs Gereben[5], Brian W. Kim[1], Peter A. Kopp[6], Xiao Hui Liao[7], Maria Jesus Obregon[8], Robin P. Peeters[9], Samuel Refetoff[7], David S. Sharlin[10], Warner S. Simonides[11], Roy E. Weiss[7] and Graham R. Williams[12]



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Massachusetts General Hospital
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60 Years of Advancing Research to Improve Health
Research supported by NIDDK