Thyroid Physiology

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Thyroid development

Thyroid anatomy

Synthesis, storage and release of thyroid hormones

Iodothyronine deiodinases

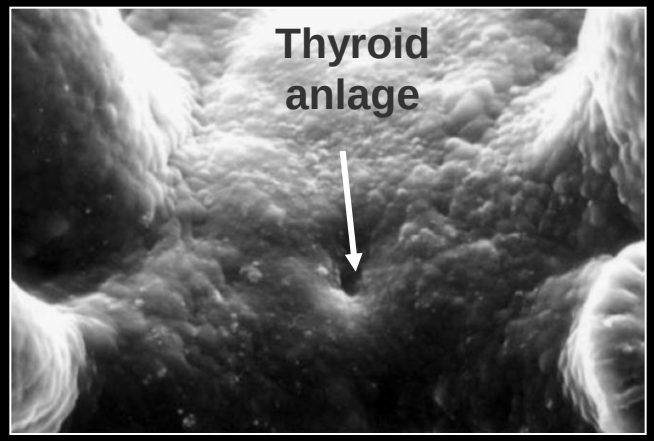
Physiological role of the thyroid hormones

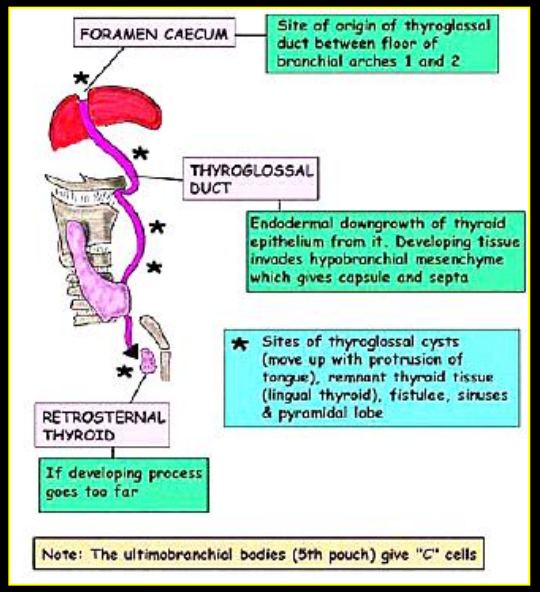
Mechanism of T3 action

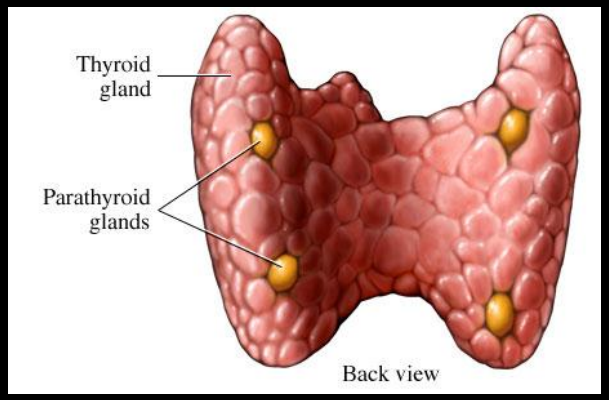
Regulation of thyroid hormone

Thyroid development

Genetics of thyroid gland development







Originates as outpouching of pharyngeal floor

Descends anterior to trachea (Ectopic thyroids lie anywhere on path)

Bifurcates to form 2 lateral lobes connected by the isthmus

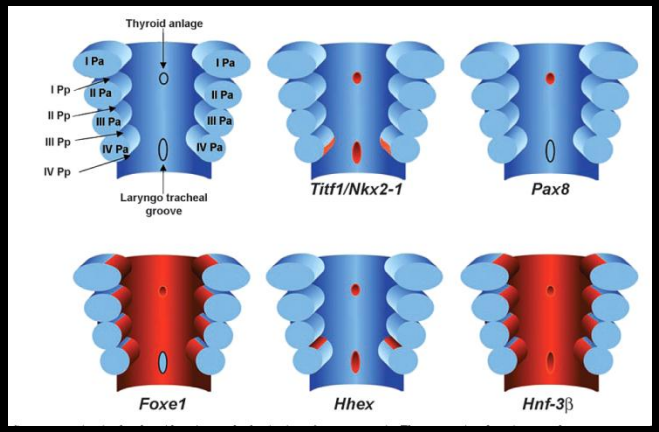
Recurrent laryngeal nerves run behind the gland

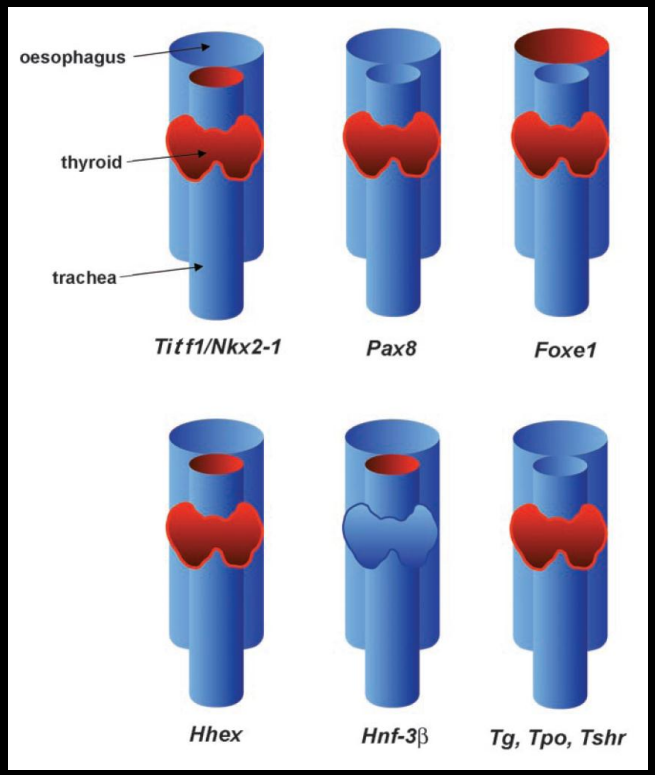
Parathyroids lie behind the upper and middle parts of each lobe.

0.1% neuroendocrine parafollicular C-cells that secrete calcitonin

(Felice and Di Lauro 2004 Endocrine Reviews 25:722–746)

Genetics of thyroid gland development





Early stages of organogenesis

Titf1 (thyroid transcription factor-1) transcription factor essential for survival of precursor cells and for Tg, TPO expression

Pax8 (paired box gene 8) Trascription factor required for formation of thyroid follicular cells and expression of Foxe1 and Hhex. Required to initiating and maintaining tissue-specific gene expression.

Foxe1 (forkhead box E1) winged helix/forkhead transcription factors plays an essential role in promoting migration and regulation of Tg and TPO.

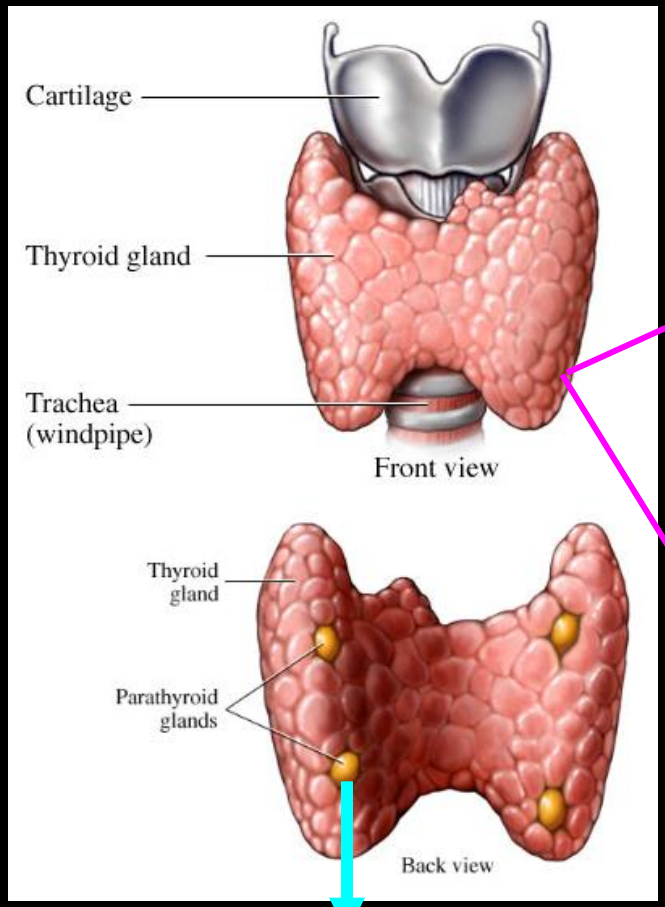
Hhex (hematopoietically expressed homeobox) transcription factor essential for thyroid morphogenesis. Required to maintain expression of Titf1 and Foxe1 and Pax8, But Titf1 and Pax8 are required to maintain Hhex expression also.

Late stages of organogenesis

TSHR (TSH receptor) Not required for migration or folliculogenesis. Required for completion of differentiation, proliferation and function (expression of NIS and TPO)

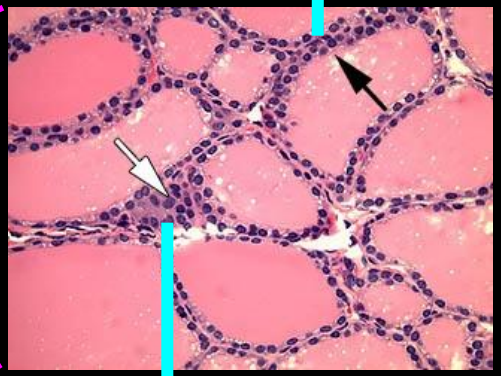
(Felice and Di Lauro 2004 Endocrine Reviews 25:722–746)

Hormone synthesis by the thyroid and parathyroids



T3 and T4

Follicular cells



Parafollicular C-cells

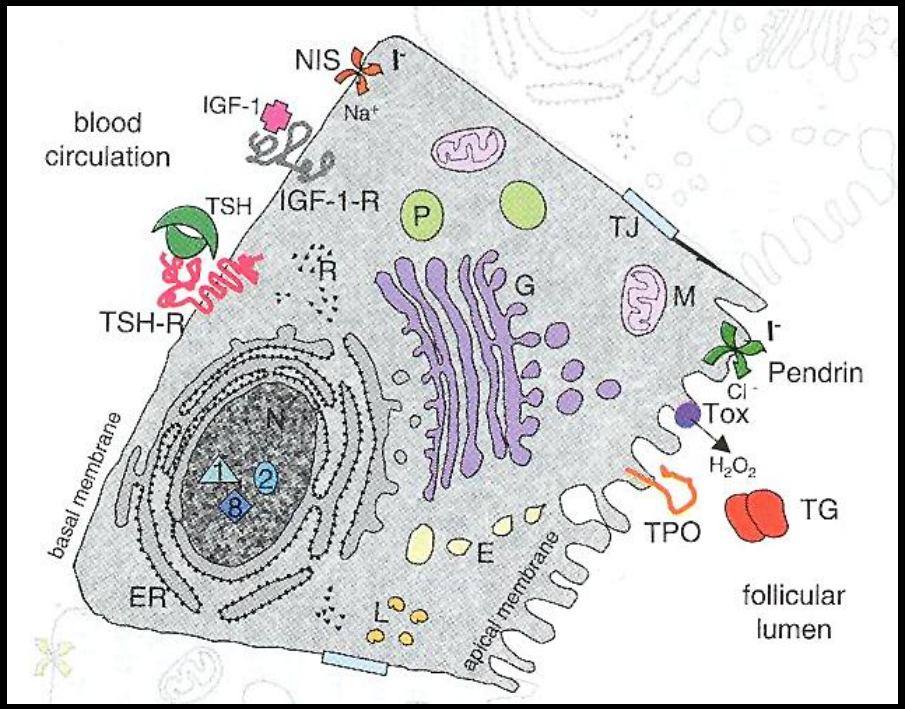
Calcitonin

Parathyroid hormone

Thyroid hormone synthesis and metabolism

Iodothyronine synthesis

T4 is a pro-hormone and T3 is the active ligand



Thyroid follicular cell

1. Active transport of iodide into the thyrocyte and follicular lumen (NIS, Pendrin)

2. Generation of H_2O_2 (Duox1/2)

3. Oxidation of iodide and iodination of tyrosyl groups in thyroglobulin (TPO)

4. Coupling of pairs of iodotyrosine molecules to form iodothyronines (TPO)

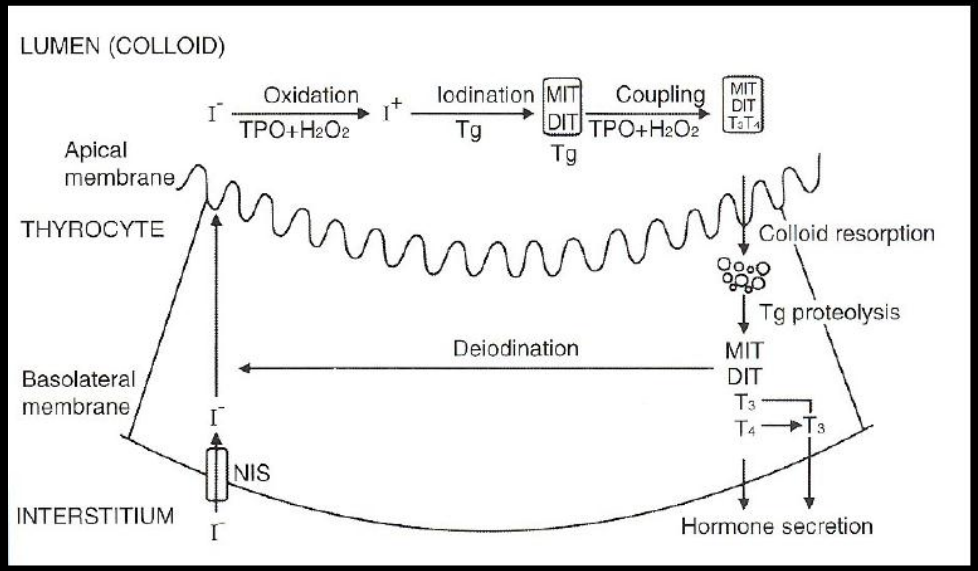
5. Proteolysis of thyroglobulin to release iodothyronines into circulation

6. 5'-deiodination of T4 to T3 in peripheral cells (D1, D2)

Iodothyronine synthesis

Thyroglobulin

- large glycoprotein of 2 subunits (5496 amino acids)
- Secreted into follicular lumen
- 140 of the amino acids are tyrosyl residues
- Coupling of pairs of iodotyrosine molecules to form iodothyronines
- 4 tyrosyl residues are correctly positioned to allow hormonogenesis



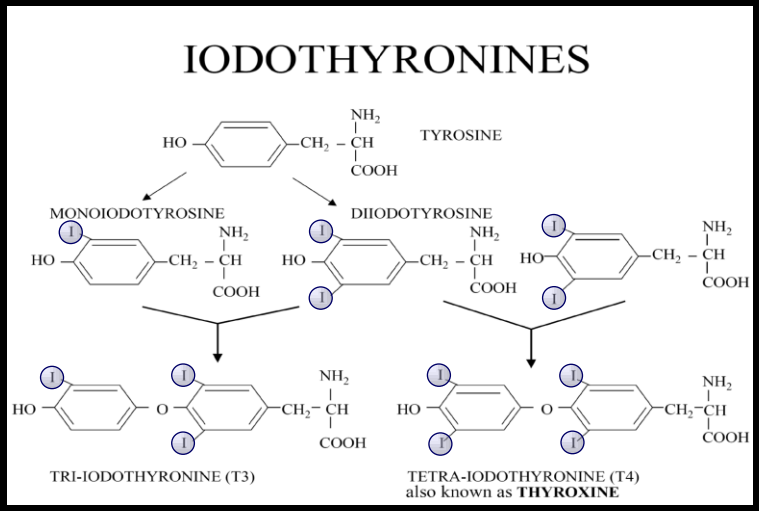
Oxidation of iodide and iodination of tyrosyl groups in thyroglobulin

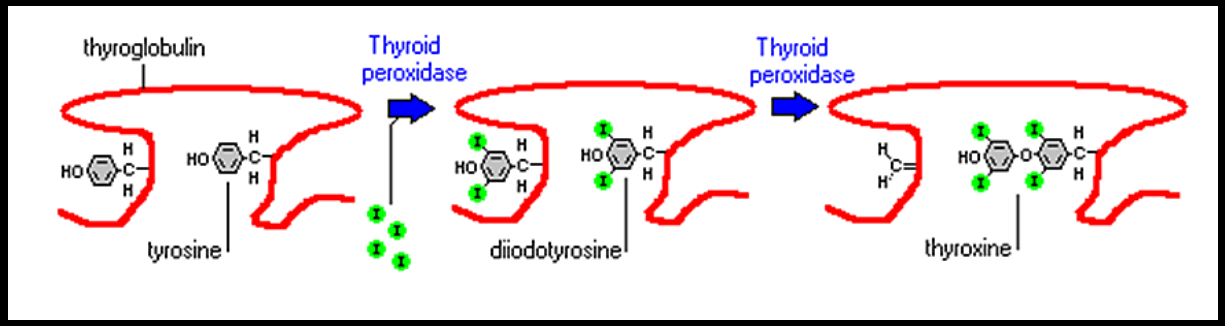
- **H_2O_2 is generated by Tox complex that includes Duox1 and 2**

Thyroid peroxidise (TPO) uses H_2O_2 to oxidise iodide

- **I^+ intermediate reacts with tyrosyl residues of thyroglobulin (MIT/DIT)**

Coupling of of tyrosyl residues





Coupling of 2 pairs of tyrosyl residues is catalysed by TPO

- Coupling of MIT and DIT forms T3
- Coupling of DIT and DIT forms T4

Proteolysis of thyroglobulin releases T4 and T3 into circulation

Residual DIT and MIT are deiodinated and iodide conserved

T3 is generated from T4 in peripheral cells by 5'-deiodination

Thyroid hormones transport and metabolism

10 times more total T4 in plasma than T3

- Free T4 9-26 pmol/l (Half life 7 days)
- Free T3 2.5-5.7 pmol/l (Half life 1 day)

Transported in blood bound to plasma proteins

	T4	T3
Thyroid binding globulin	68%	80%
Transthyretin	11%	9%
Albumin	20%	11%
Unbound	0.05%	0.5%

Thyroid hormone metabolism

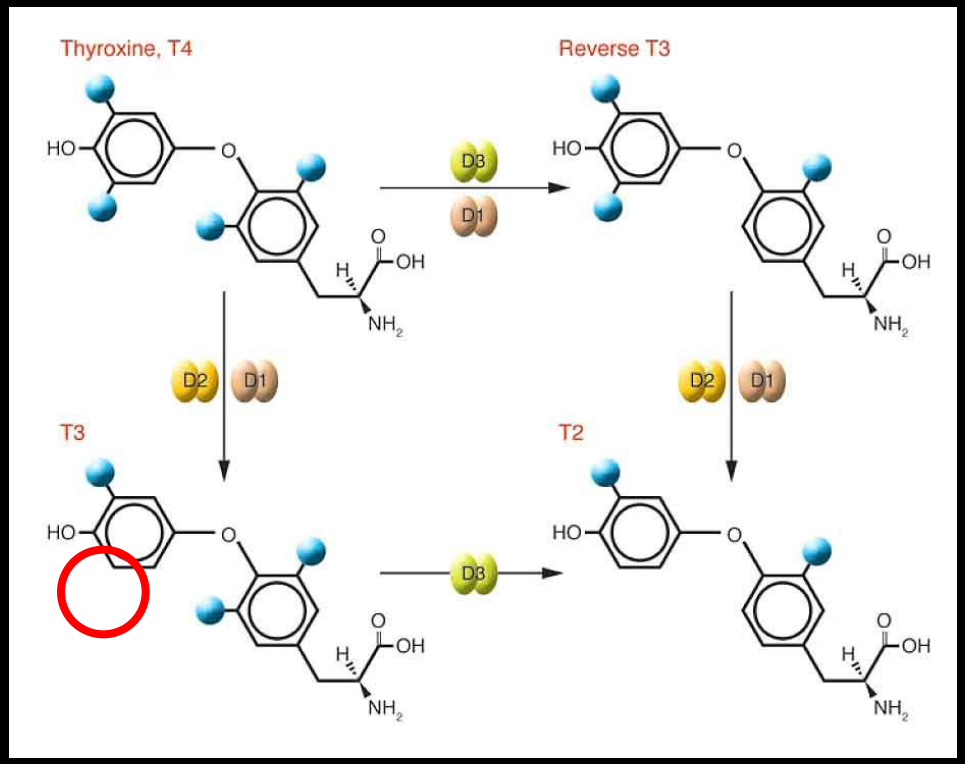
- Deiodination T4 and T3 in liver by (D1)
- Deamination and conjugation (Glucuronidation)

Free and conjugated forms excreted in bile & urine

Iodine is recycled to thyroid

The iodothyronine deiodinases

ProhormoneT4 is converted to the active ligand T3 by 5' deiodination
Deiodinases are selenoproteins with selenocystine in active site



T4 to T3 conversion
Type 1 and type 2 iodothyronine deiodinases (D1, D2)

Circulating T3
predominantly by liver D1 and muscle D2

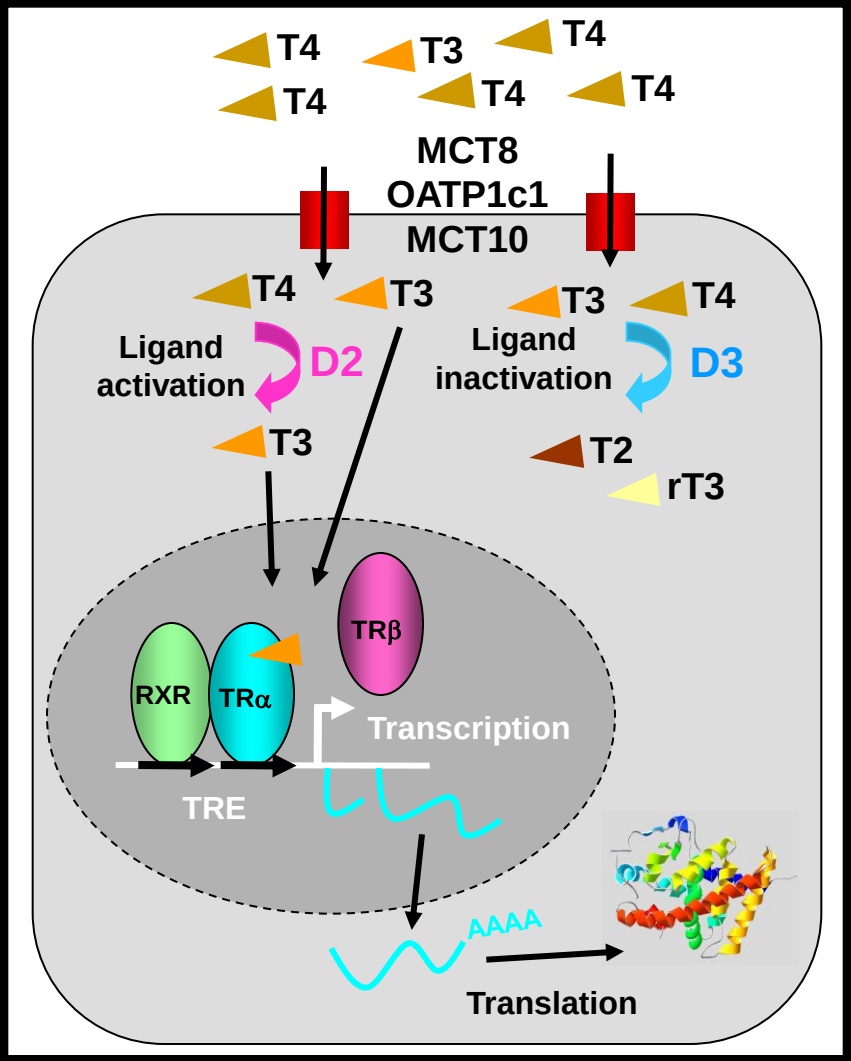
T3/T4 inactivated by 5 deiodination
Type 3 iodothyronine deiodinase

Intracellular ligand supply
Regulated by relative local expression of D2 and D3

D1 and D3 activity is increased by thyroid hormone
D2 activity is inhibited by thyroid hormone

Bianco AC (2006). J. Clin. Invest. 116:2571–2579.

Thyroid hormone transport and deiodination



High specificity active TH transporters

Monocarboxylate transporters

MCT8

MCT10

Organic anion-transporting polypeptide

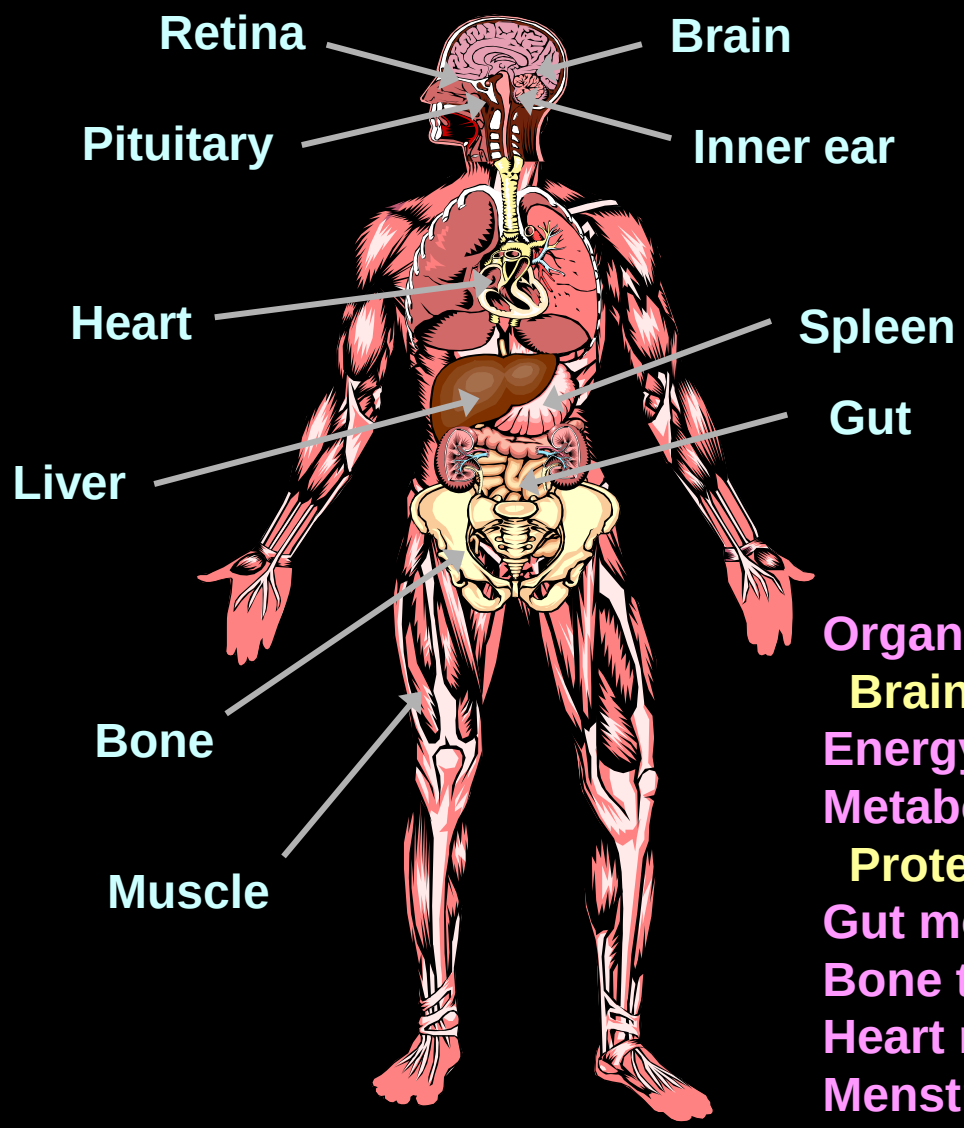
OATP1c1

(Visser WE 2007 Trend Endocrinol Metab 19:50)

Thyroid hormone action

Major thyroid hormone target tissues

Thyroid hormone promotes differentiation and inhibits proliferation



BMR
Thermogenesis
Adipogenesis
Vasculature
Skin
Hair
Bone marrow
Kidney
Lung

Organogenesis
- **Brain, eye, ear and bone**

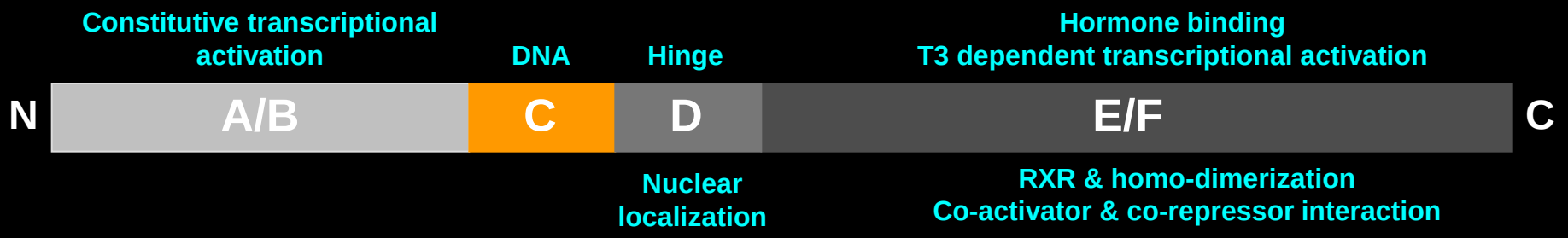
Energy expenditure
Metabolism
- **Protein/carbohydrate/fat**

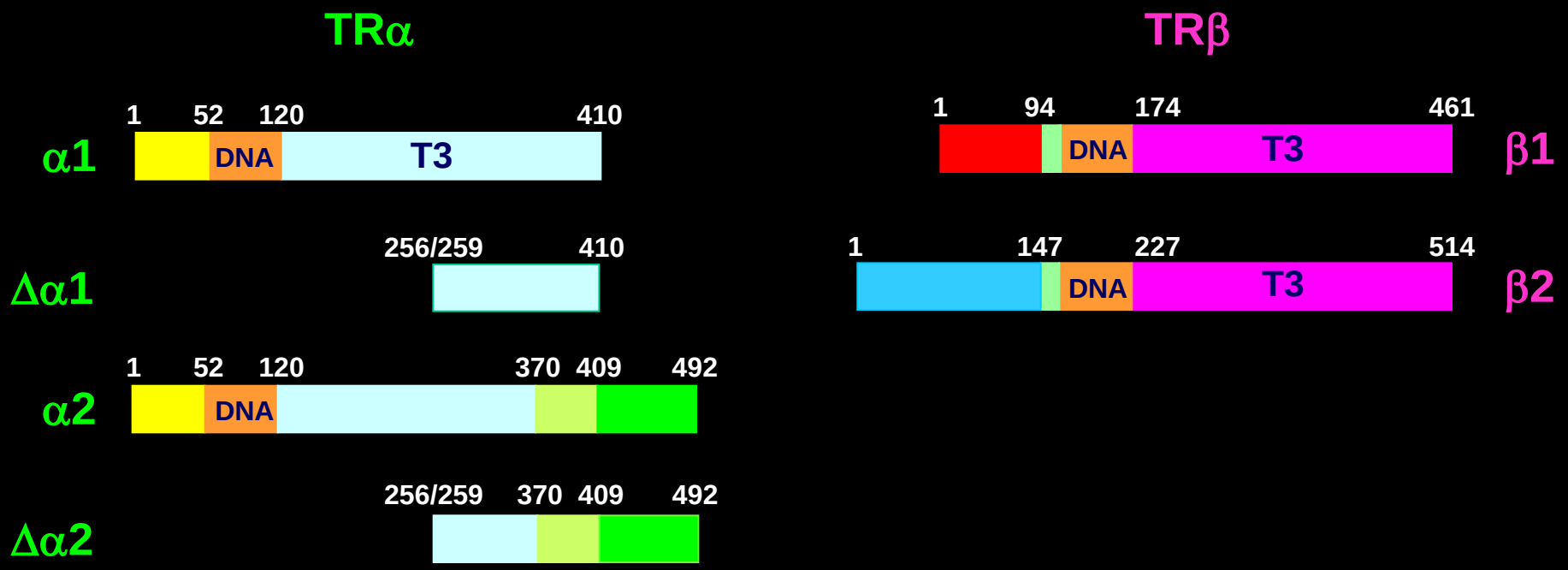
Gut motility
Bone turnover
Heart rate and contractility
Menstrual cycle

Tissue specific effect of thyroid hormones

- **Cardiovascular**
  - Increases rate and contractility reduces peripheral vascular resistance
- **Bone**
  - Linear growth, peak bone mass and bone remodelling cycle
- **Sympathetic nervous system**
  - Increases β-adrenergic receptor expression
  - Amplifies responses to ADR and NA (CNS and neuromuscular)
- **CNS development**
  - Cerebella, cortical, cochlear and retina
- **Skeletal muscle**
  - Myogenesis and repair
  - Increased muscle contraction and relaxation (brisk reflexes/tremor)
- **Gastrointestinal**
  - Increase gut motility
- **Energy and lipid metabolism**
  - Increased basal metabolic rate
- **Liver**
  - Increased gluconeogenesis and glycogenolysis, cholesterol synthesis and degradation
- **Endocrine**
  - GnRH secretion, prolactin secretion, cortisol metabolism, aromatase
- **Hematopoietic**
  - Increases erythropoietin

Thyroid hormone receptors
TRα and β isoforms





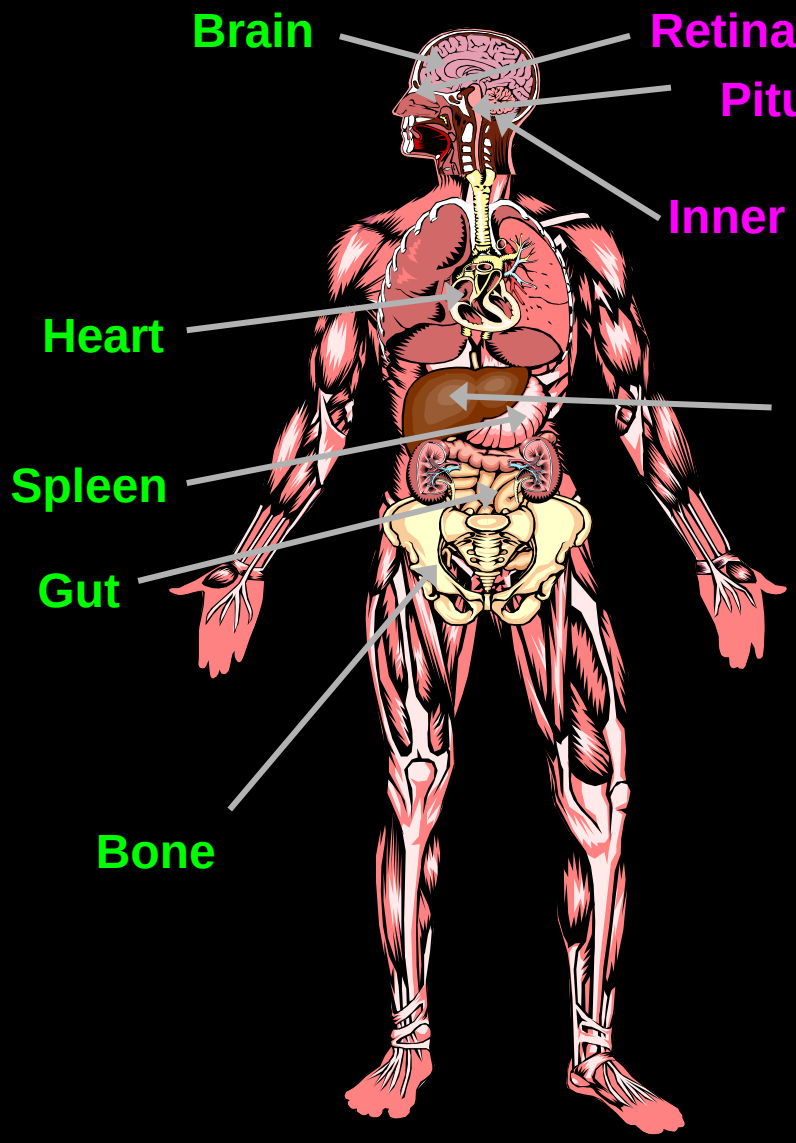
Thyroid hormone receptors act as transcriptional repressors and T3-inducible transcription factors

- Multiple TR isoforms of TRα and TRβ
  - TRα1 and TRβ1 and β2 are true receptors
  - TRα2, Δα1 and Δα2 may act as antagonists
- TRs are constitutively localized to the nuclear
- TRs bind to TREs of varying structure in gene promoters
- TRs bind co-repressors, co-activators and other nuclear proteins
- Unliganded apo-TR is a repressor
- T3-stimulated positive or negative regulation of T3 target genes
  - Positive TREs in *GH*, *DIO1*, *ME*, *MHC* genes
  - Negative TREs in *TRH*, *TSHB* genes

TR isoform-specific target tissues

TRα

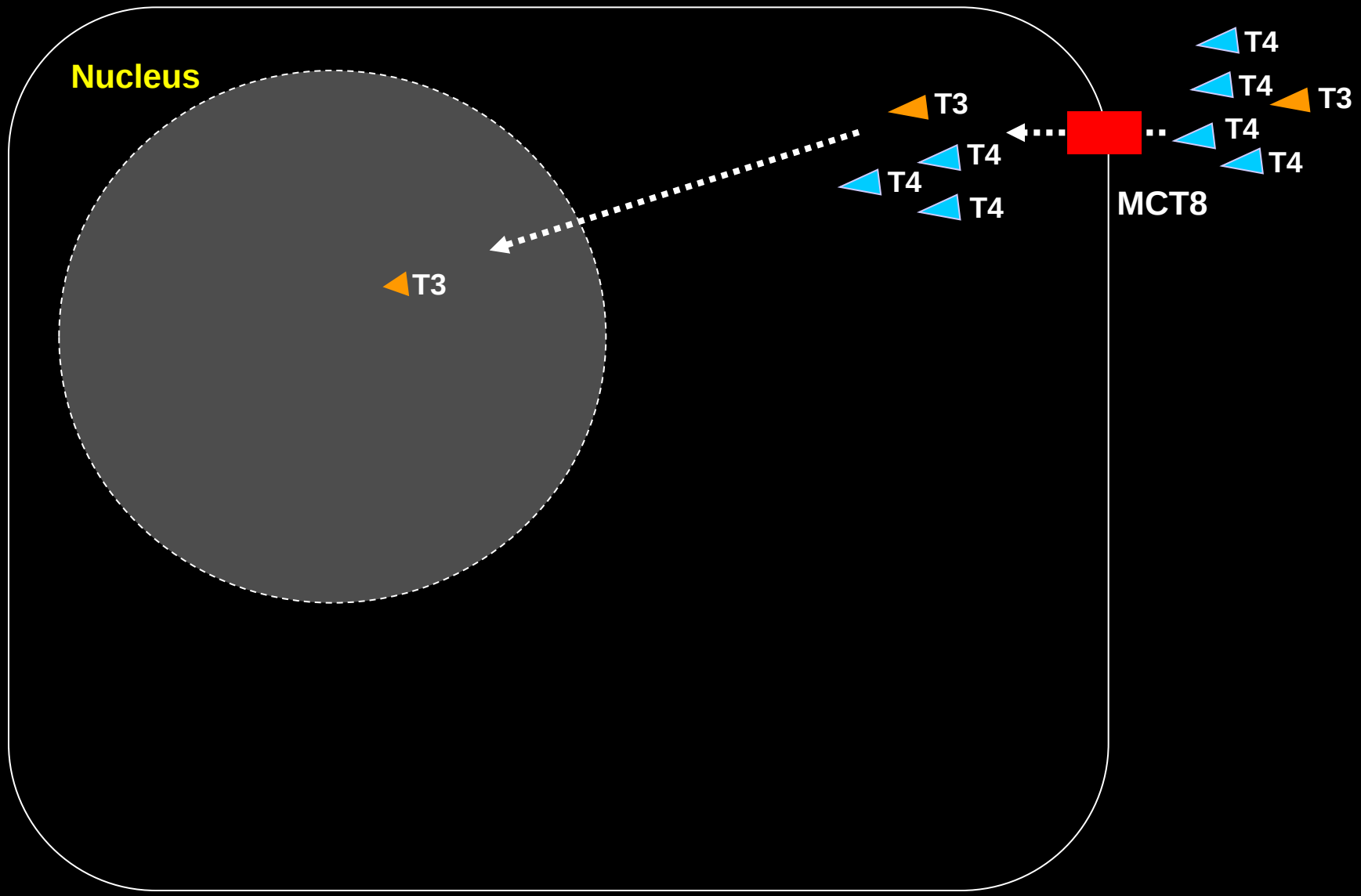
TRβ



Mixed TRα and TRβ or unknown

- BMR
- Thermogenesis
- Adipogenesis
- Vasculature
- Skin
- Hair
- Muscle
- Bone marrow
- Kidney
- Lung

Thyroid hormone action



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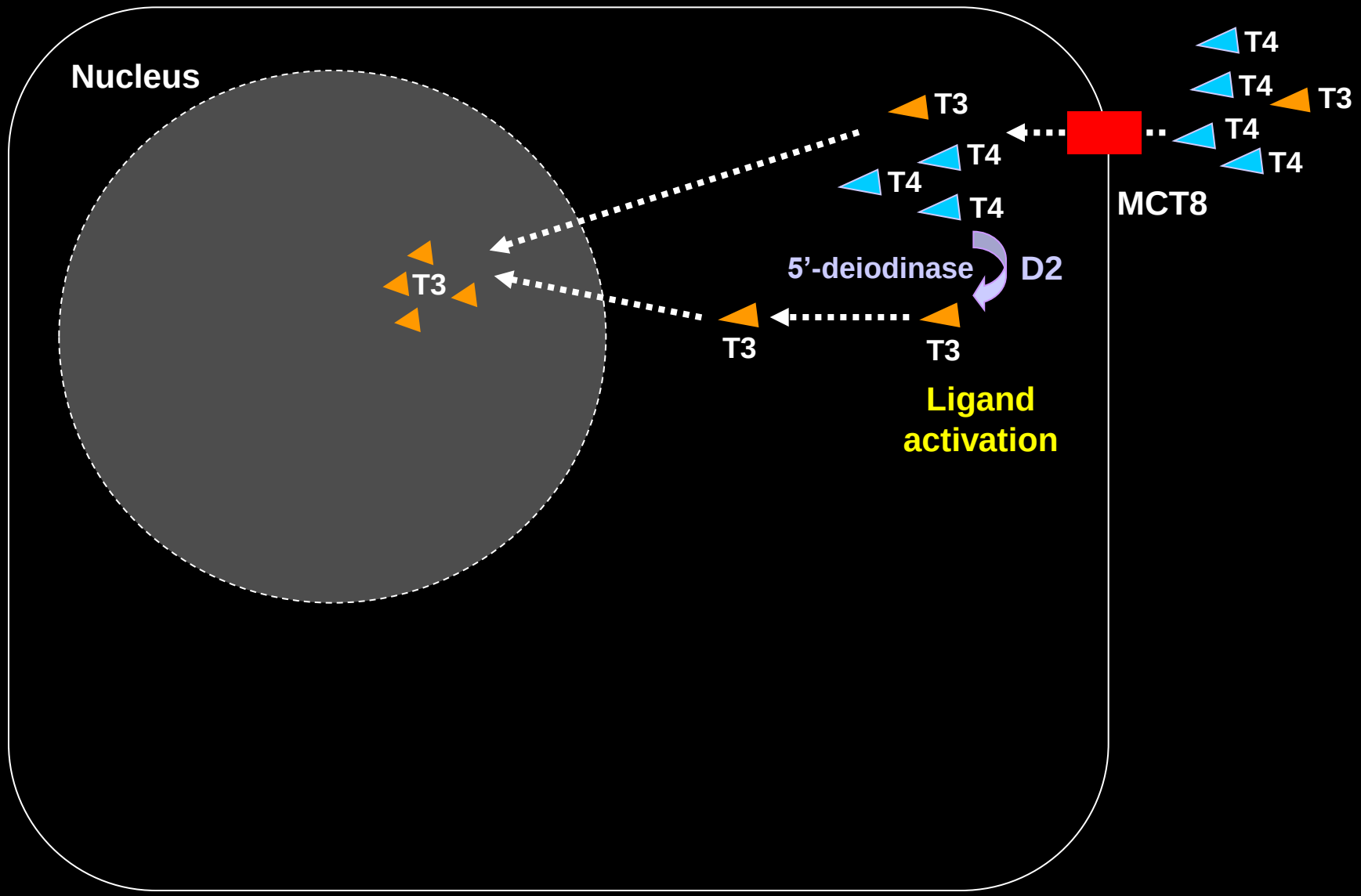
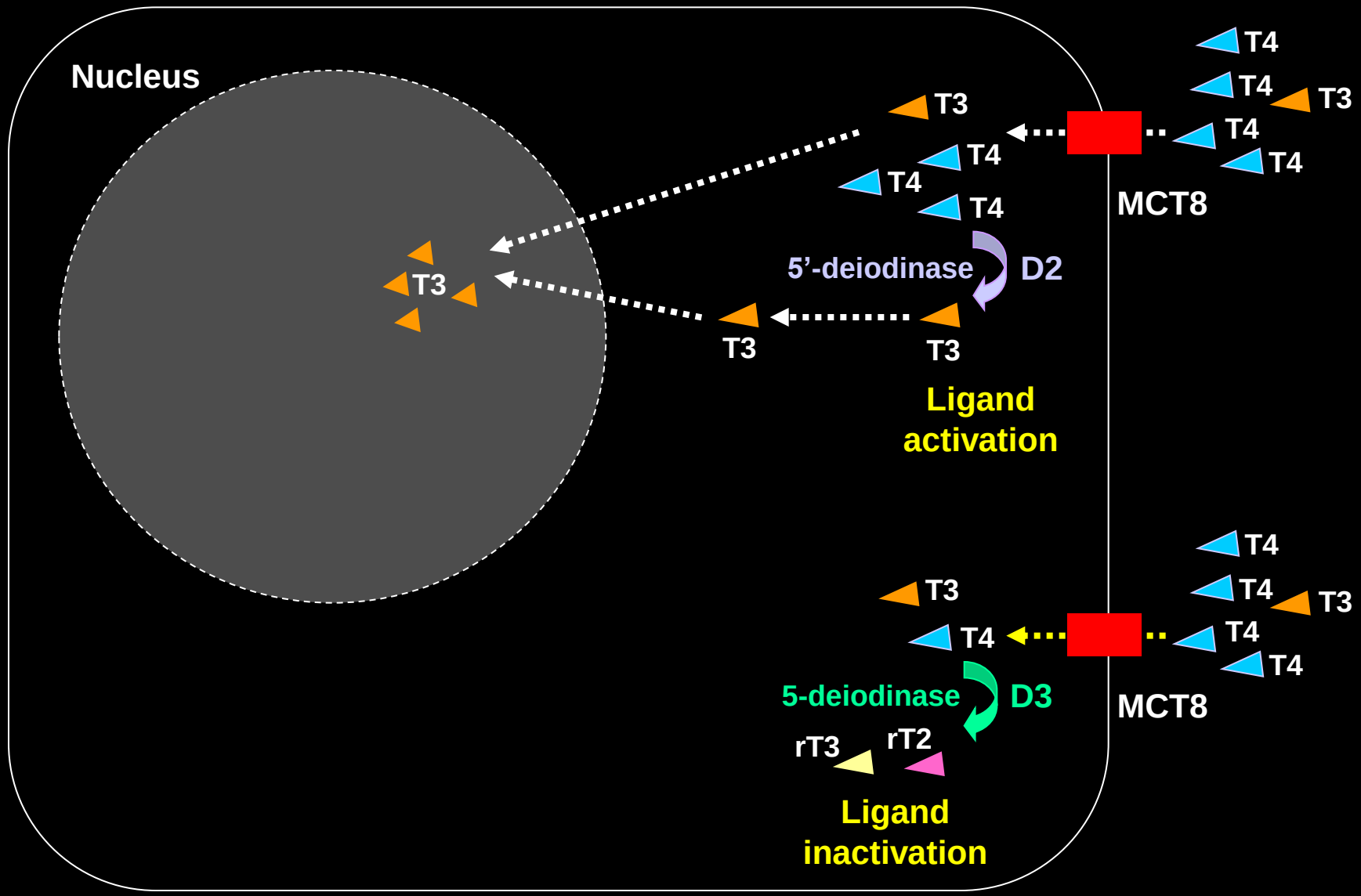
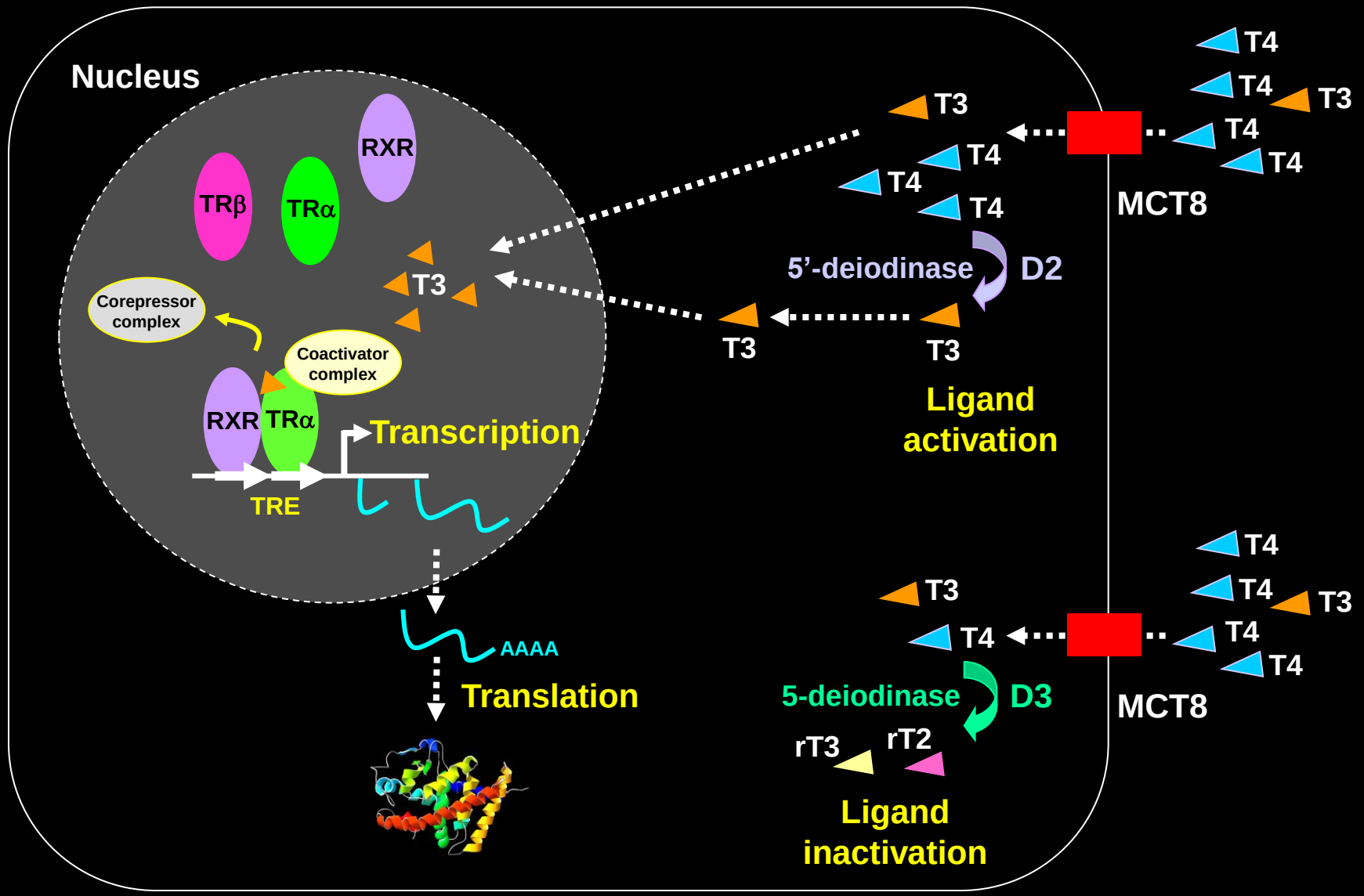


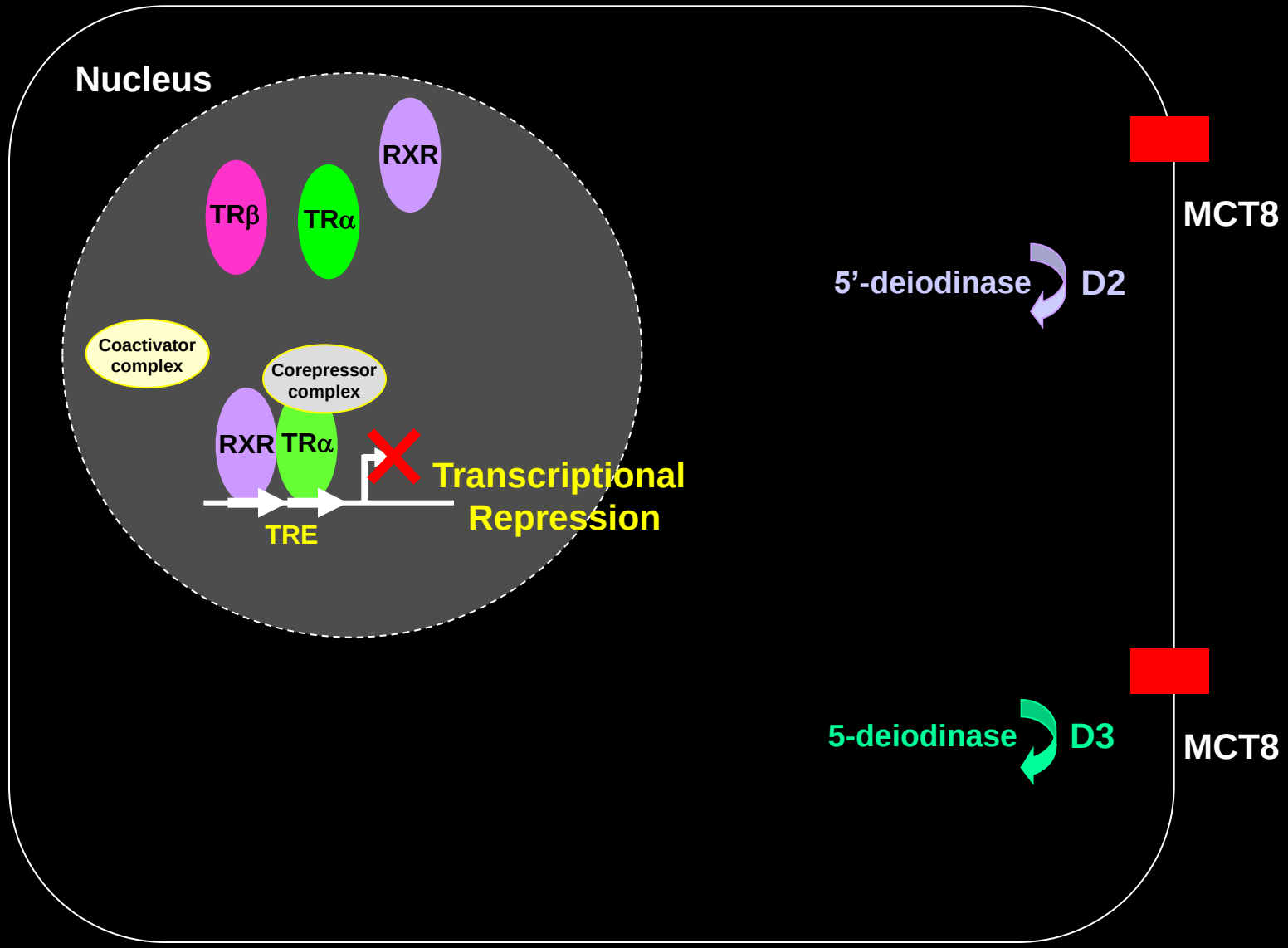
Thyroid hormone action



Thyroid hormone action

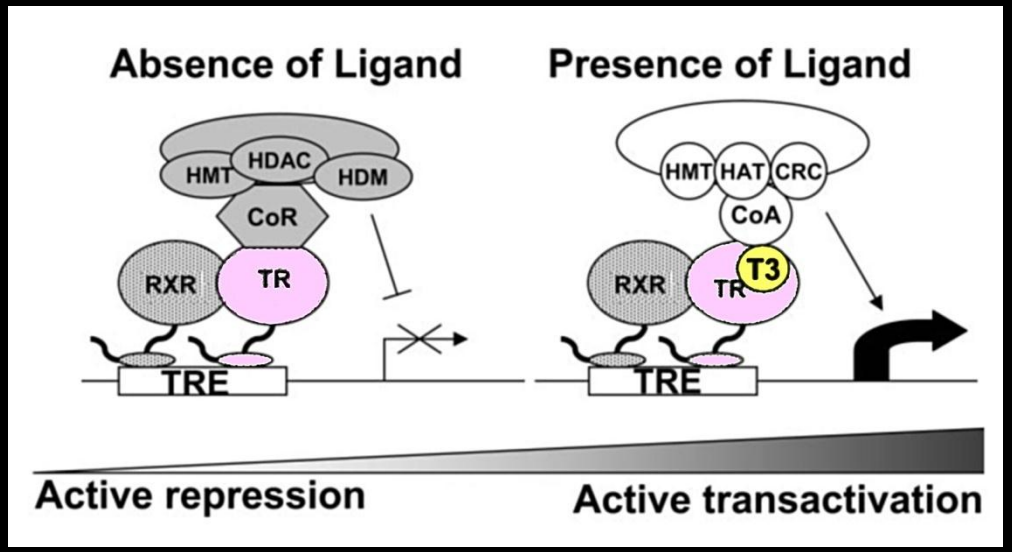


Unliganded apo-TRs are repressors



Regulation of target genes with positive TREs

TR binds to TRE either as homodimer or heterodimer with RXR.



In absence of T3 the TR recruits

- **Co-repressor molecules**
- **Histone methyl transferase, histone deacetylase and histone demethylase**
- **Interfere with the basal transcription machinery**

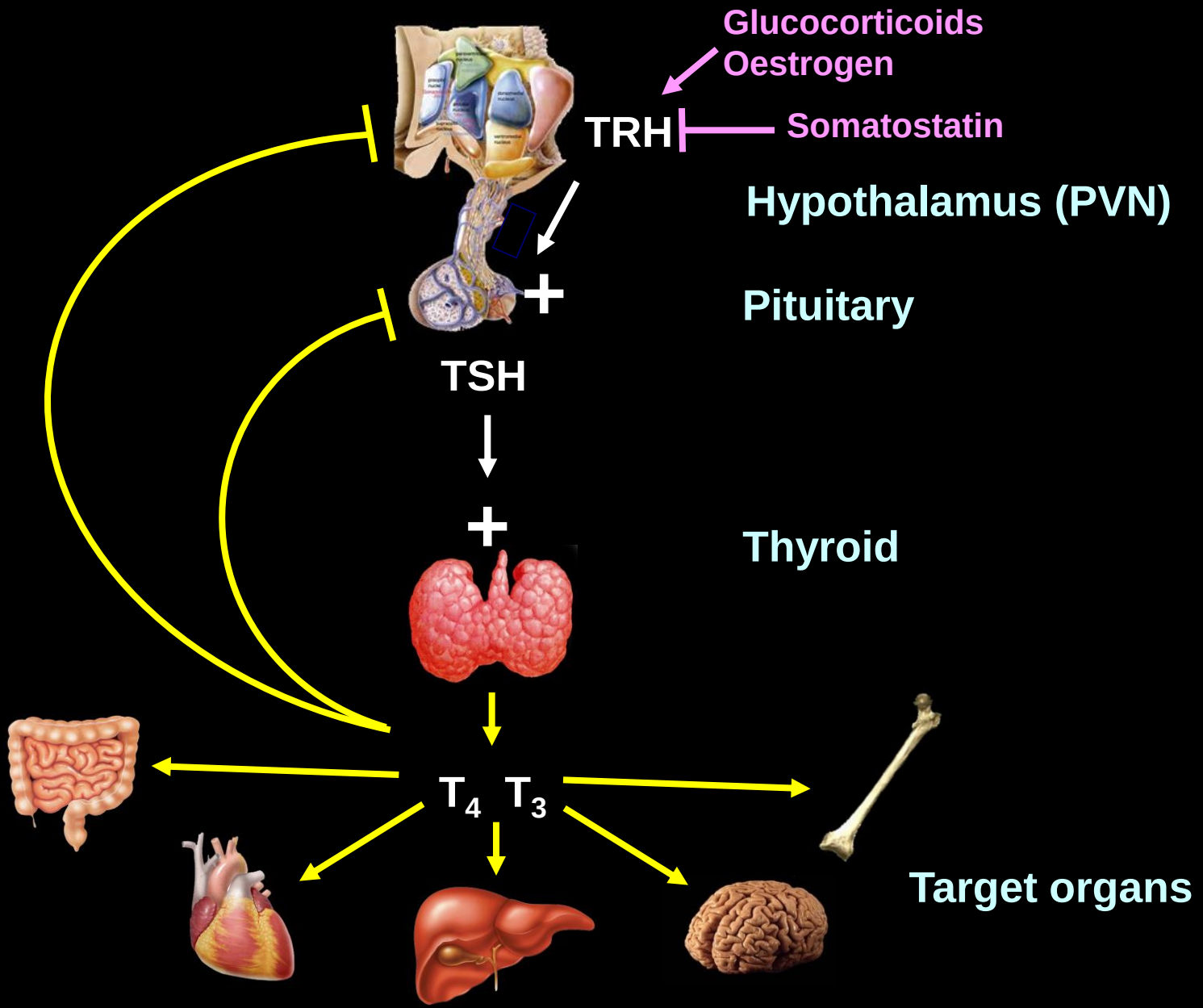
T3 binding to TR results in co-repressor release

- **Recruitment of co-activators**
- **Histone arginine methyltransferase; histone acetyl-transferase;**
- **Chromatin remodeling complex**
- **Directly interaction with basal transcription machinery and transcription**

(Flamant F 2007 Molecular Endocrinol 21:321)

Regulation of thyroid hormone synthesis and secretion

Hypothalamic-pituitary-thyroid axis



Thyrotropin releasing hormone (TRH)

Synthesised by TRH neurons of the paraventricular nucleus of hypothalamus

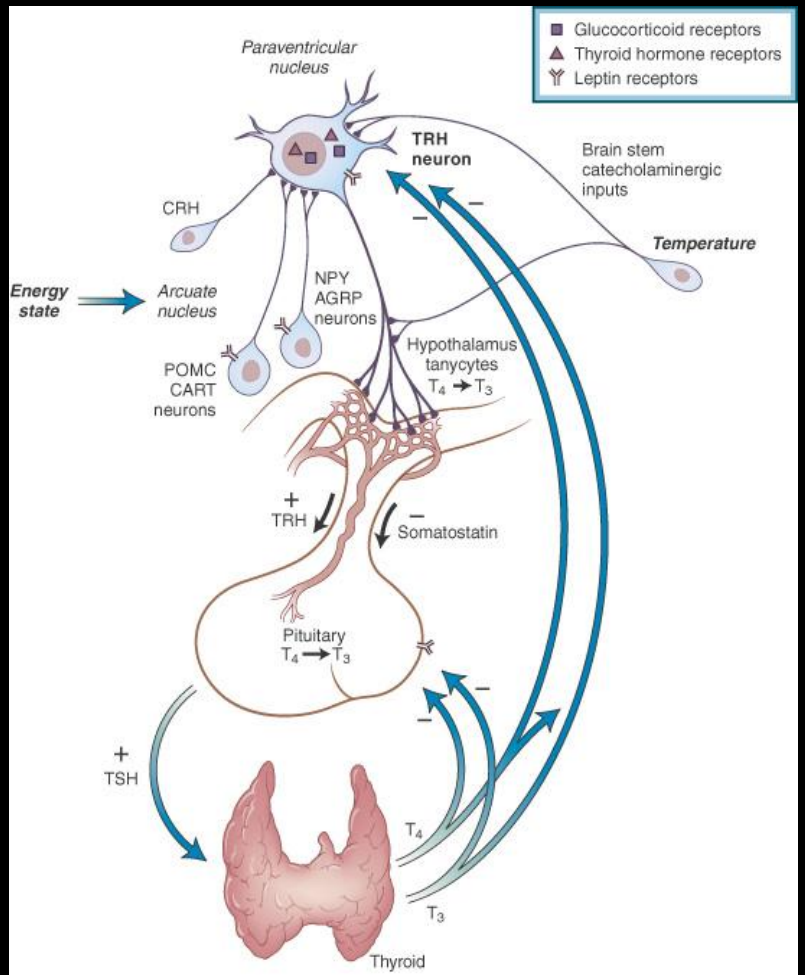


Figure 7–9. Regulation of the hypothalamic-pituitary-thyroid axis. *AGRP*, Agouti-related protein; *CART*, cocaine- and amphetamine-regulated transcript; *CRH*, corticotropin-releasing hormone; *NPY*, neuropeptide Y; *POMC*, proopiomelanocortin; T_3, triiodothyronine; T_4, thyroxine; *TRH*, thyrotropin-releasing hormone; *TSH*, thyrotropin.

Negative feedback regulation

T4 accesses the TRH neurons via the CSF
T3 accesses TRH neurons via BBB
- **T4 is the key regulator of TRH**

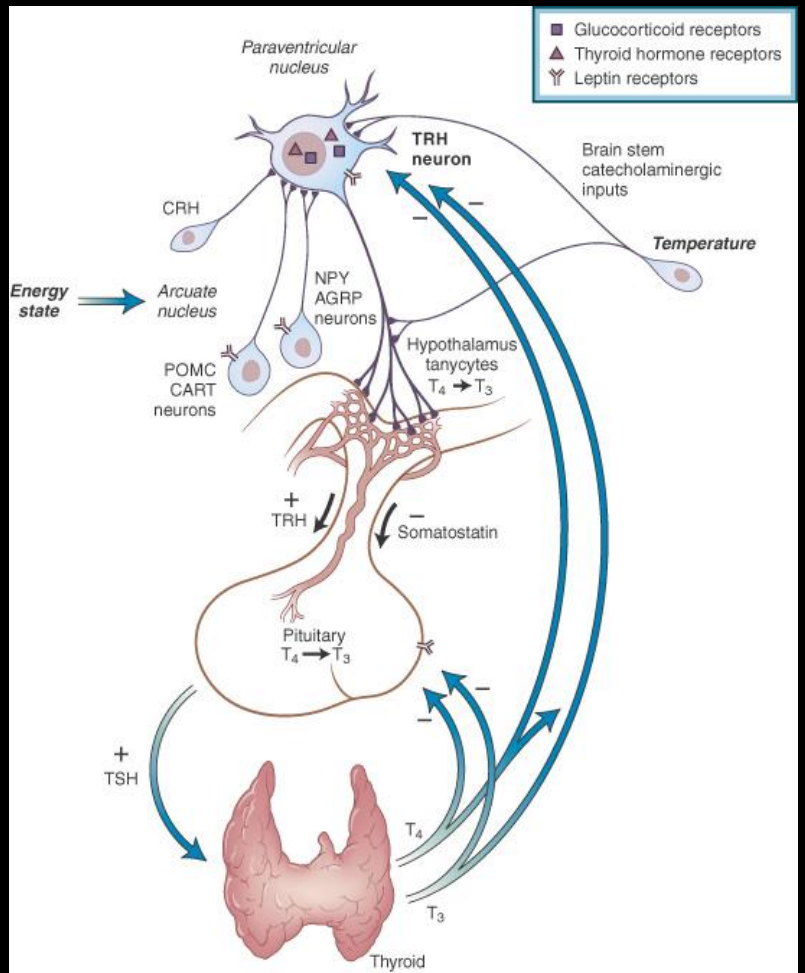
D2 converts T4 to T3
- **T3 and acts via TRβ2 to inhibit TRH synthesis.**

TRH is a tri-peptide
- **Six copies of pyroGlu-His-Pro in TRH peptide**
- **Protein convertases PC1 and PC2 cleave**
- **Acts via the portal venous system**

TRH receptor is G-protein coupled receptor
- **TRHR expressed in thyrotrophs & lactotrophs**

Actions of TRH
- **Transcription of α and β subunits of TSH**
- **Post translational glycosylation of TSH (determines TSH potency and half life)**

Thyrotropin releasing hormone (TRH)



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Neural regulation of TRH

Circadian rhythm
TRH stimulates pulsatile release of TSH (peak 2am, minimum 5pm)

Temperature
Cold exposure increases TSH secretion (Sympathetic Adr, NA)
Also involves somatostatin NPY, dopamine and serotonin neurons

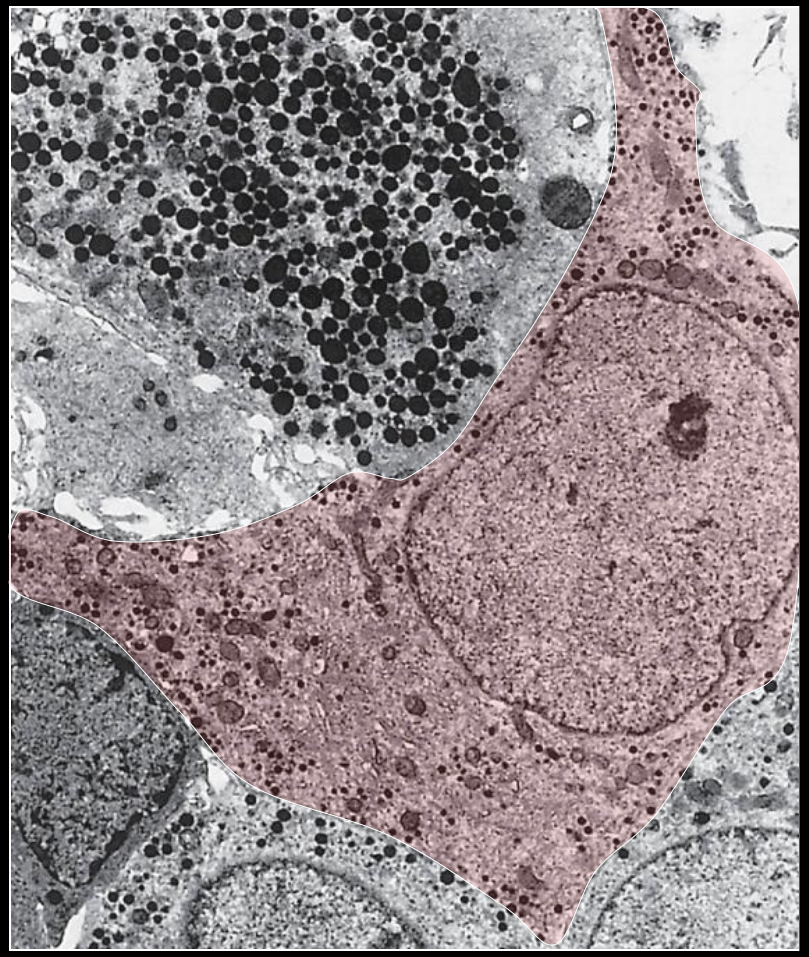
Stress (sick euthyroid syndrome)
Reduced TSH secretion
Glucorticoids may increase or decrease by direct and indirect actions

Starvation
Reduces TSH secretion
Leptin acts on TRH neurons and POMC/NPY

Infection and inflammation
IL-1 , IL-6, TNF-α inhibit TRH and TSH secretion

Thyroid stimulating hormone (TSH)

Synthesised by pituitary thyrotrophs

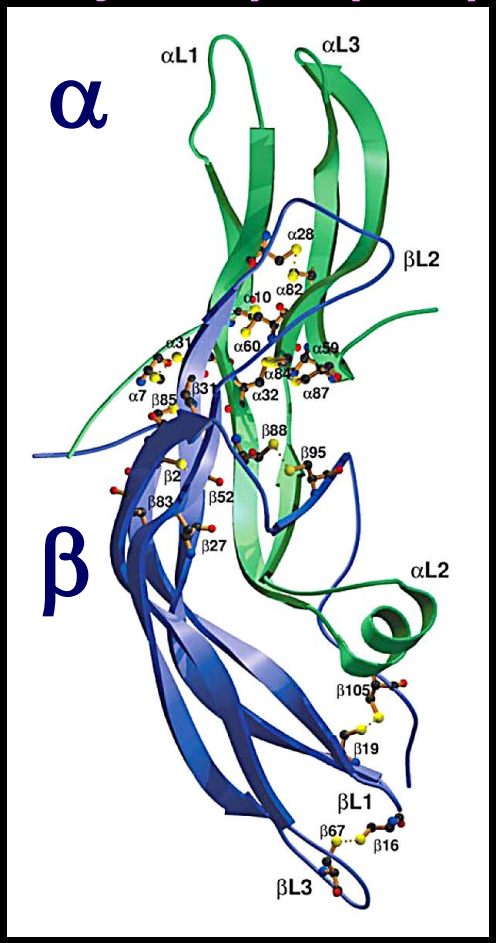


- 5% of anterior pituitary cells are thyrotrophs
  - small secretory granules
- Stimulation of TSH secretion
  - TRH
- Inhibition of TSH secretion
  - T4 is converted to T3 by D2 in thyrotrophs
    - (T3/TRβ2 to inhibit TSH expression)
  - Dopamine
  - Somatostatin
  - Glucocorticoids
- Circadian rhythm
  - Pulsatile and tonic secretion
  - Pulses every 3h (long $T_{1/2}$ 50 minutes)

TSHR ligands

Thyrotropin (TSH) is inversely regulated by thyroid hormones

Thyrotropin (TSH)



Normal range TSH 0.3-4.2 mU/l

- 100-400IU secreted per day (half live of 50 minutes)

Heterodimeric glycoprotein hormone family

- Common α-subunit
- Unique β-subunit (TSHβ, FSHβ, LHβ and hCGβ)

Thyroid stimulating hormone (TSH)

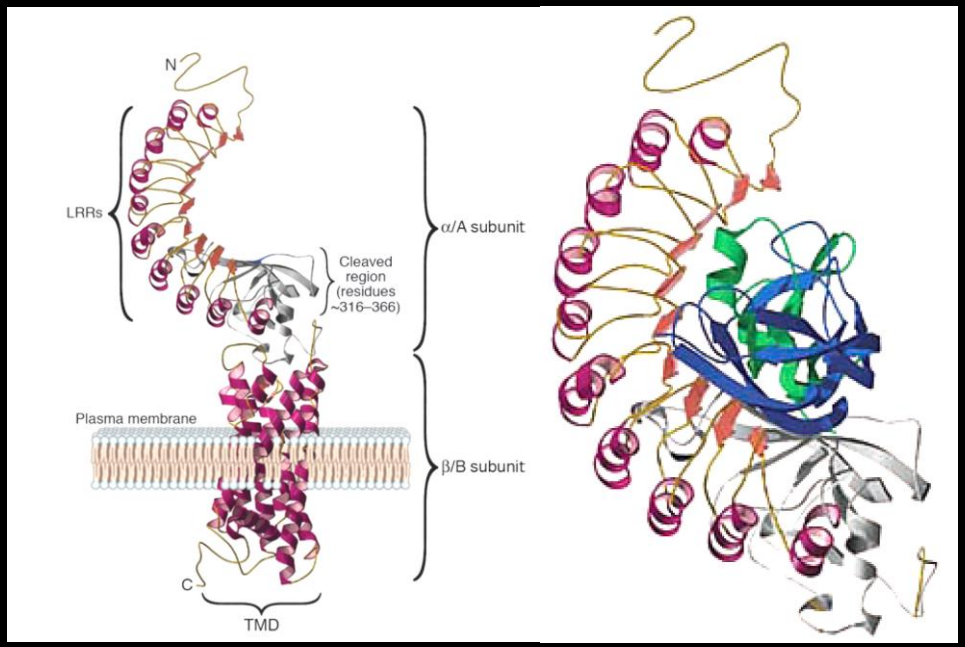
- Common 42ααα α-subunit
- Specific β-subunit 41% identity to hCG
- intrachain disulphide bonds form cysteine knot motif

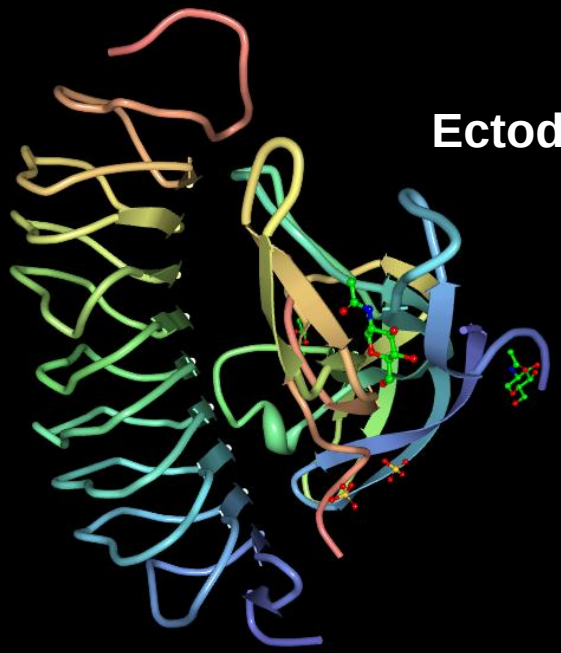
Glycosylation

- Positively regulated by TRH and negatively by T3
- Required for normal folding and potency
- Determines rate of clearance

Glinoer G 1997 Endo Rev 18:404; Nakabayashi K 2002 JCI 109:1145; Miguel RN 2004 Thyroid 12: 991

Thyroid stimulating hormone receptor





Ectodomain

Serpentine-domain (7TM)

TSHR expression

- **Thyroid, thymus, pituitary, testis, kidney, brain, heart, bone, fat and lymphocytes**

Leucine rich repeat ectodomain

- **LRRs are a 20-30αα motif of β-strand and α-helix**
- **40% homology between TSHR, LH/CGR and FSHR**

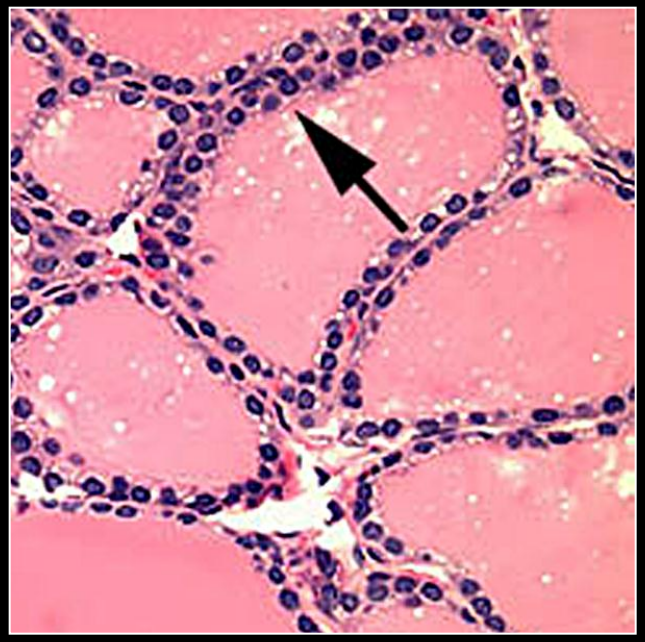
Cystein rich flanking hinge region

Heptahelical serpentine domain

- **70% homology between TSHR, LH/CGR and FSHR**

Luecke H 2001 Science 293:1449, Fan QR Nature 2005 433:269, Davies T 2005 JCI 115:1972

Regulation of thyroid follicular cells by TSH



Thyroid Follicles

TSH/TSHR signalling regulates

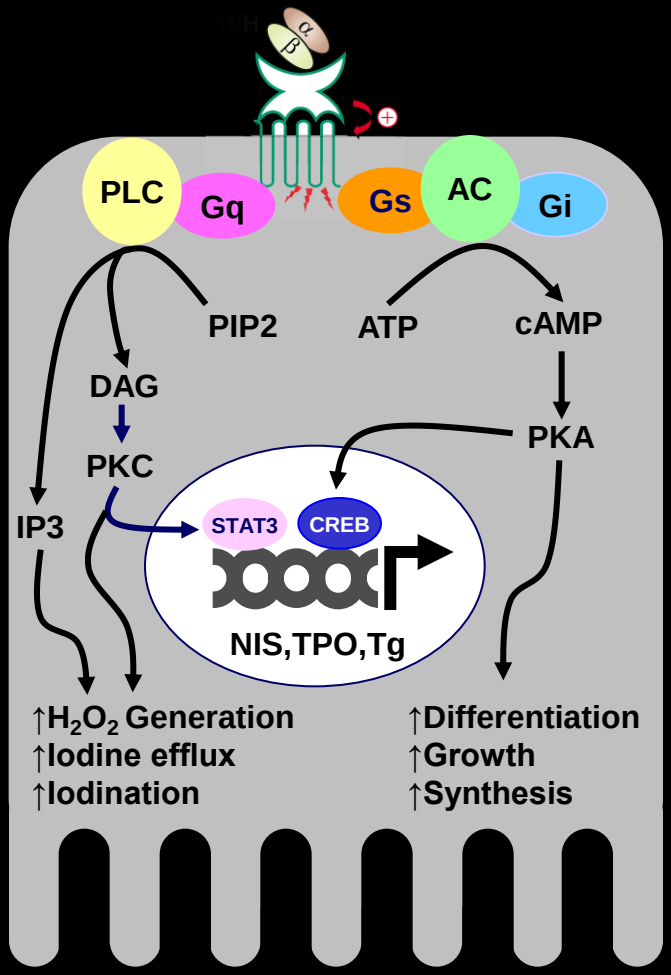
Terminal thyroid maturation and growth

Follicular cell proliferation and differentiation

Thyroid hormone synthesis
- Thyroglobulin, TPO and NIS
- Increased lysosomal activity
- Increased release of T4 and T3

TSHR signalling in follicular cells

cAMP is the predominate secondary messenger

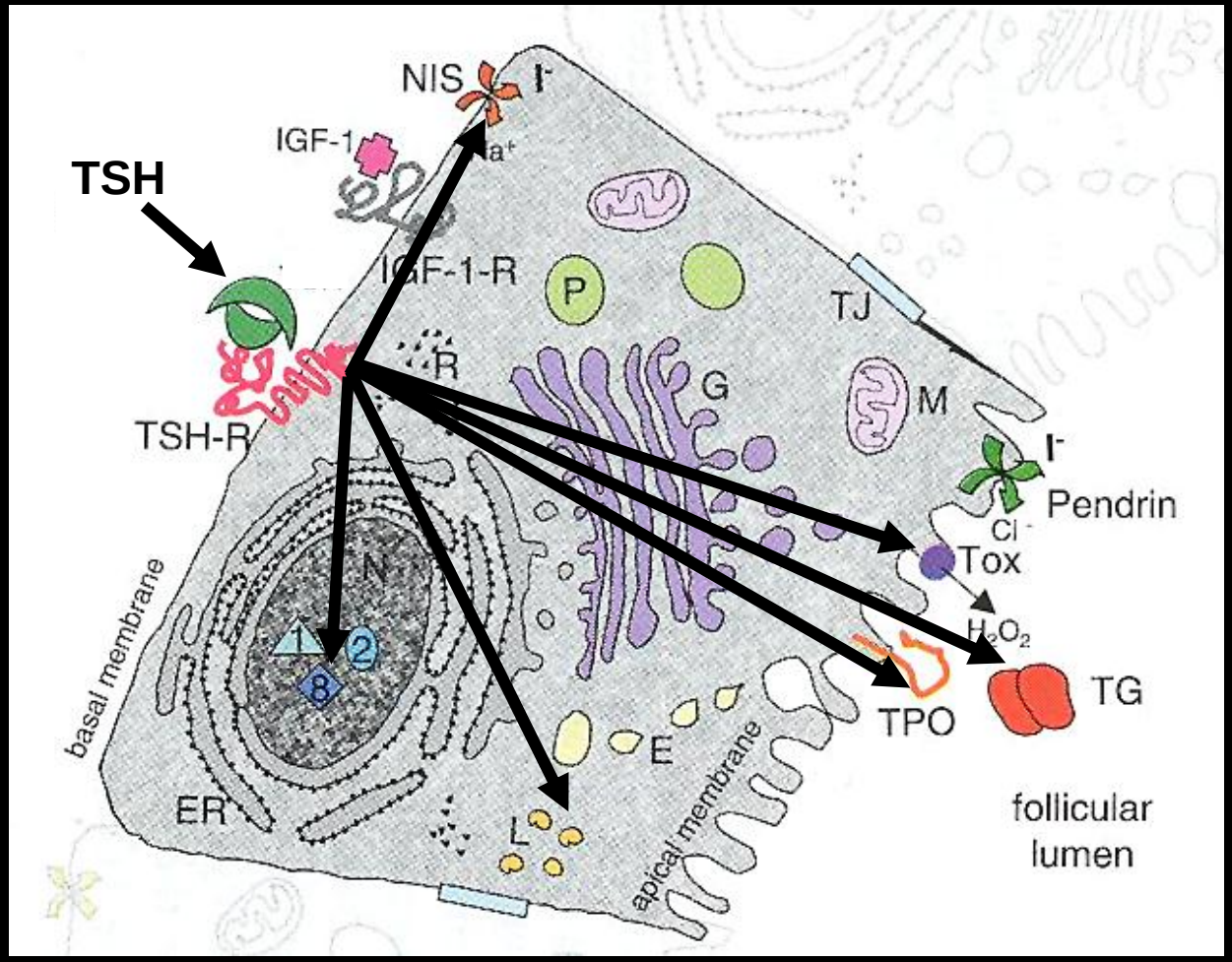


$G\alpha_s$/AC/cAMP/PKA regulates transcription of
- **Sodium-iodide symporter (NIS)**
- **Thyroid peroxidase (TPO)**
- **Thyroglobulin (Tg)**

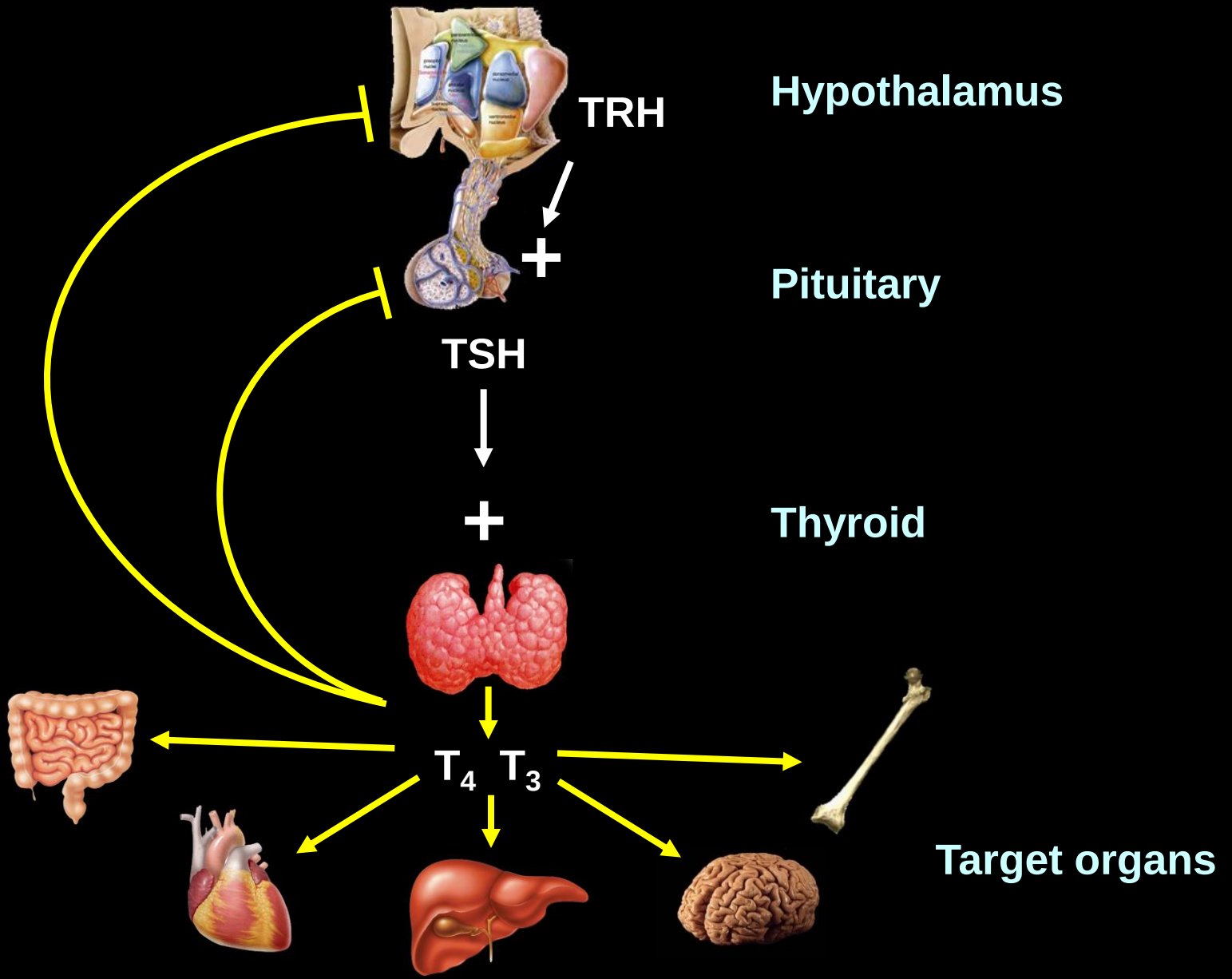
$G\alpha_q$/PLC/PKC/Ca^{2+} regulates
- **Iodine efflux**
- **Thyroglobulin iodination**
- **H_2O_2 generation (Duox)**

Kopp P 2001 CMLS 58:1301; Davies T 2002 JCI 110:161

Actions of TSH in follicular cells



Hypothalamic-pituitary-thyroid axis



References

Thyroid Physiology
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