Thyroid Physiology

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Thyroid development

Thyroid anatomy

Synthesis, storage and release of thyroid hormones

Iodothyronine deiodinases

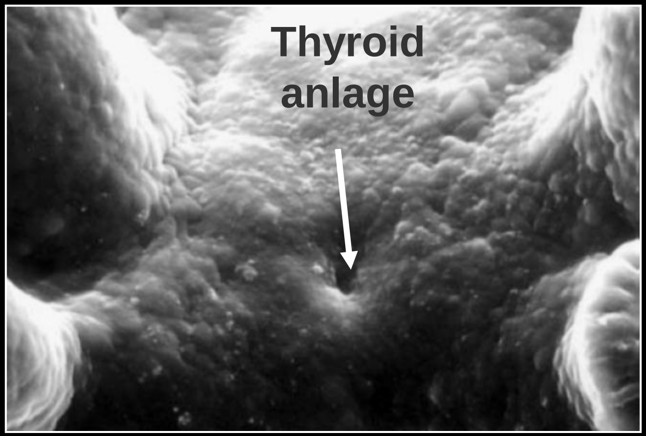
Physiological role of the thyroid hormones

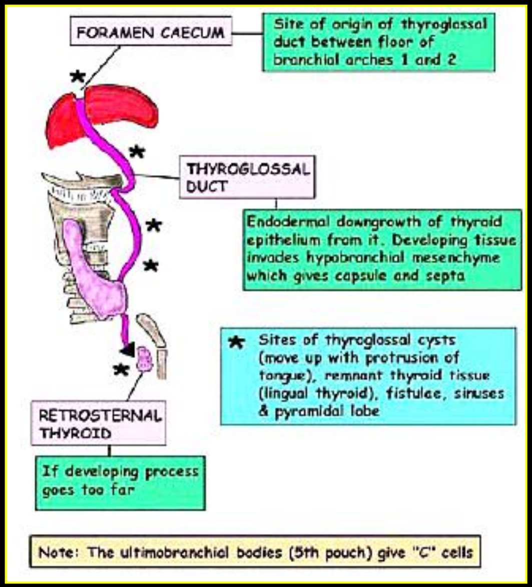
Mechanism of T3 action

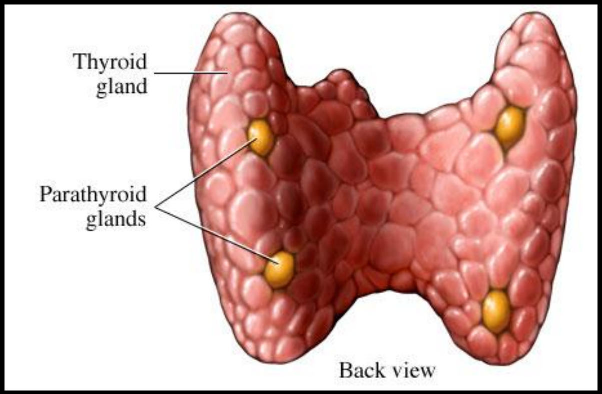
Regulation of thyroid hormone

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

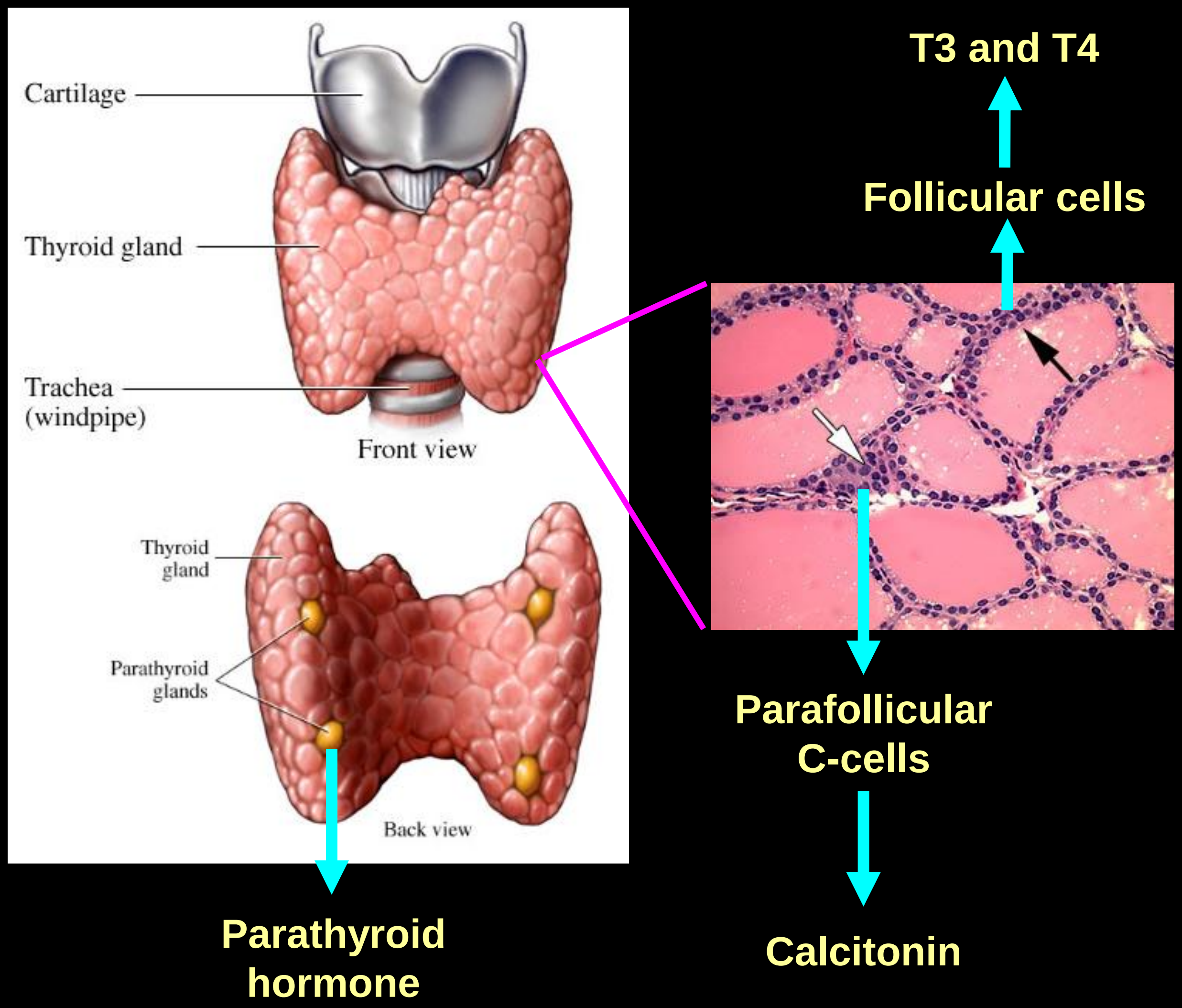
Recurrent laryngeal nerves run behind the gland

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)

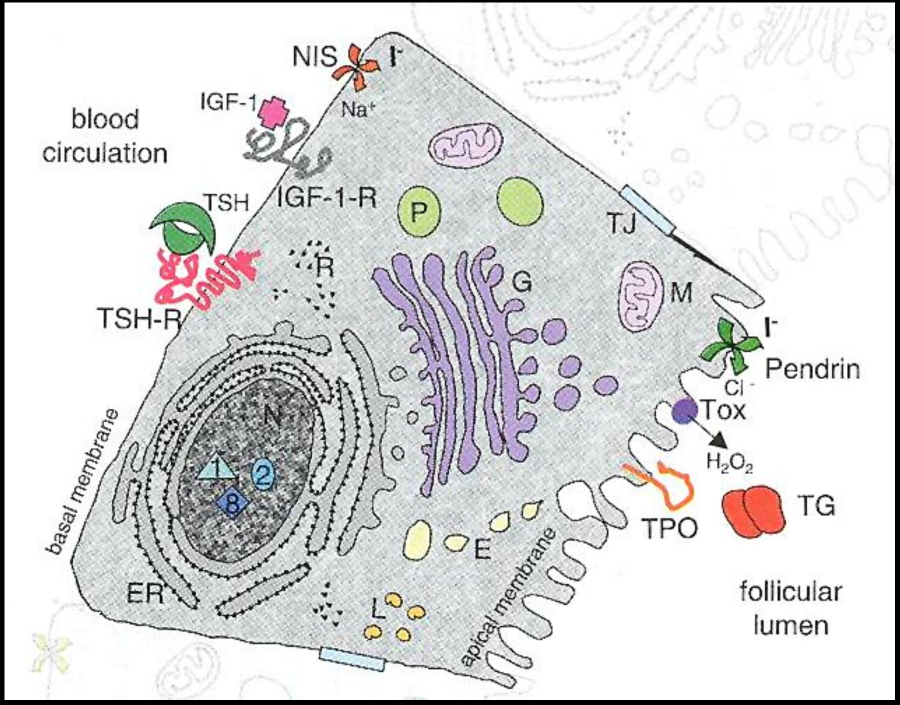
Hormone synthesis by the thyroid and parathyroids



Thyroid hormone synthesis and metabolism

Iodothyronine synthesis

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



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

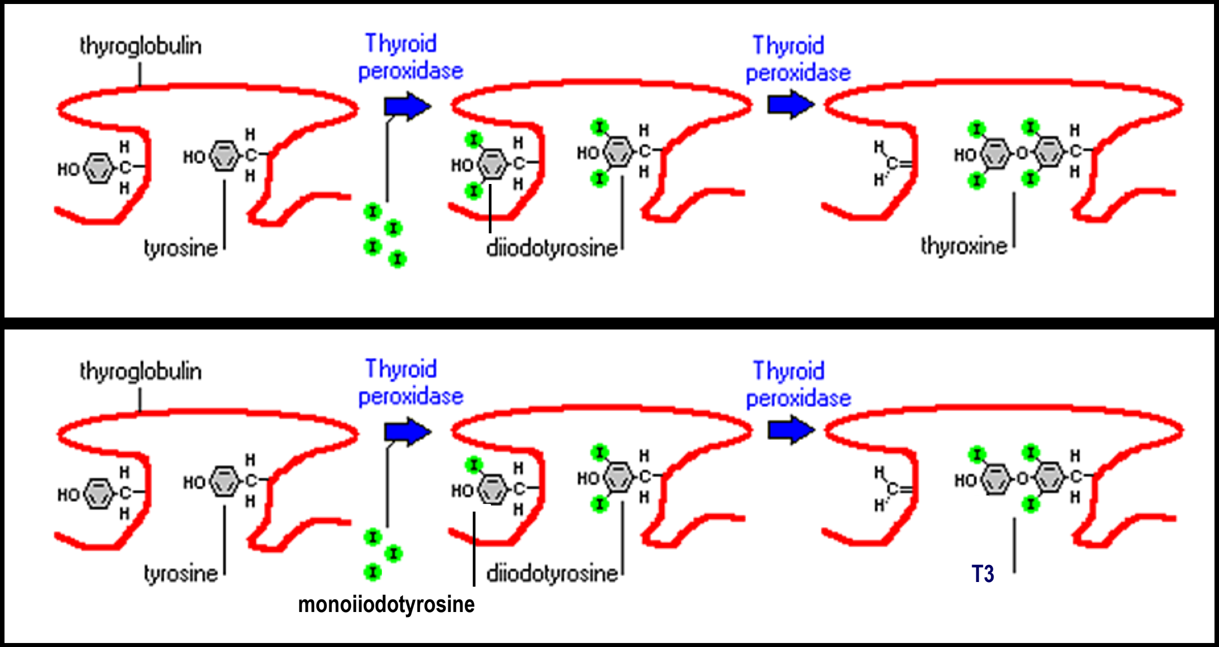
6. 5'-deiodination of T4 to T3 in peripheral cells (Dio1, Dio2)

Iodothyronine synthesis

Coupling of pairs of iodotyrosine molecules to form iodothyronines

Thyroglobulin

- **large glycoprotein secreted into follicular lumen**
- **2 subunits (5496 amino acids 140 are tyrosyl residues)**
- **4 tyrosyl residues are correctly positioned to allow hormonogenesis**



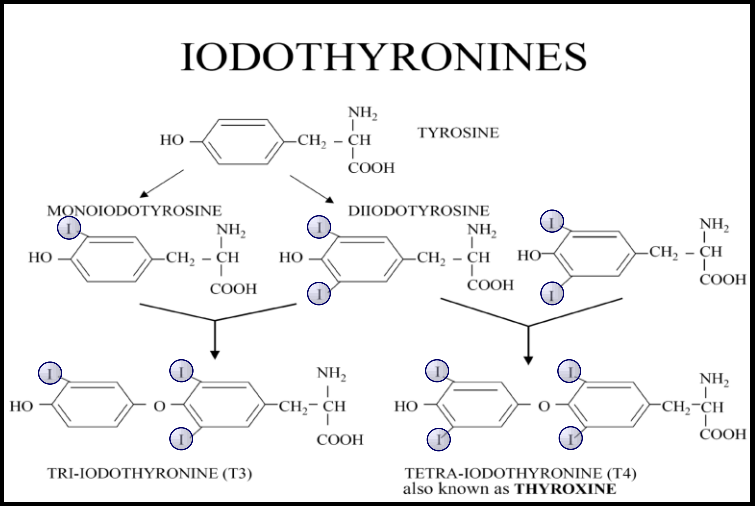
Oxidation of iodide and iodination of tyrosyl groups in thyroglobulin

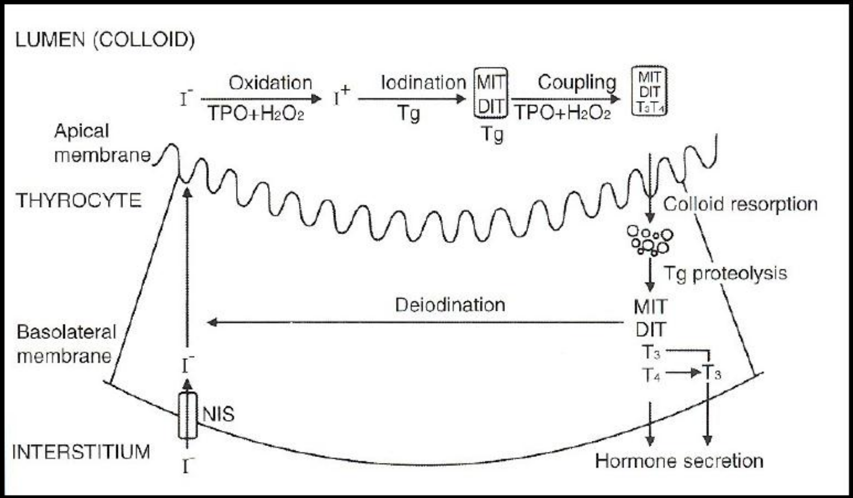
- **H_2O_2 is generated by Tox complex that includes Duox1 and 2**

Thyroid peroxidase (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

Additional 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

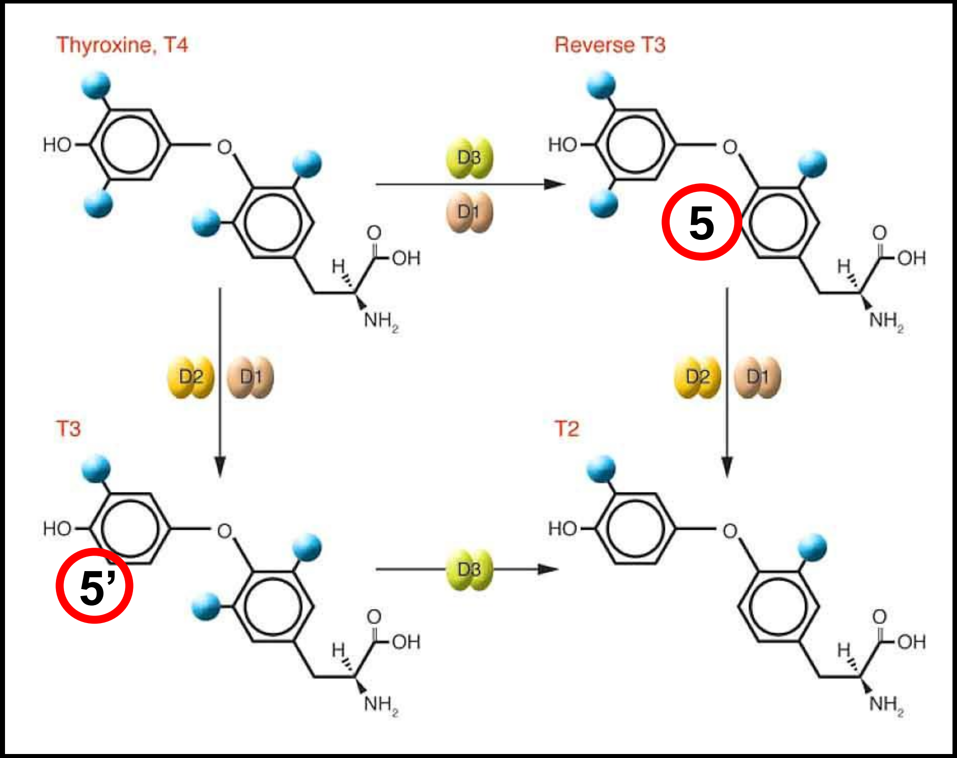
- Deiodination T4 and T3 in liver by (D1)
- Deamination and conjugation (Glucuronidation)

Free and conjugated forms excreted in bile & urine

Iodine is recycled to thyroid

The iodothyronine deiodinases

Pro-hormone T4 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) D2 more efficient

Circulating T3
Most from D1 expressed in liver
Some from D2 in muscle

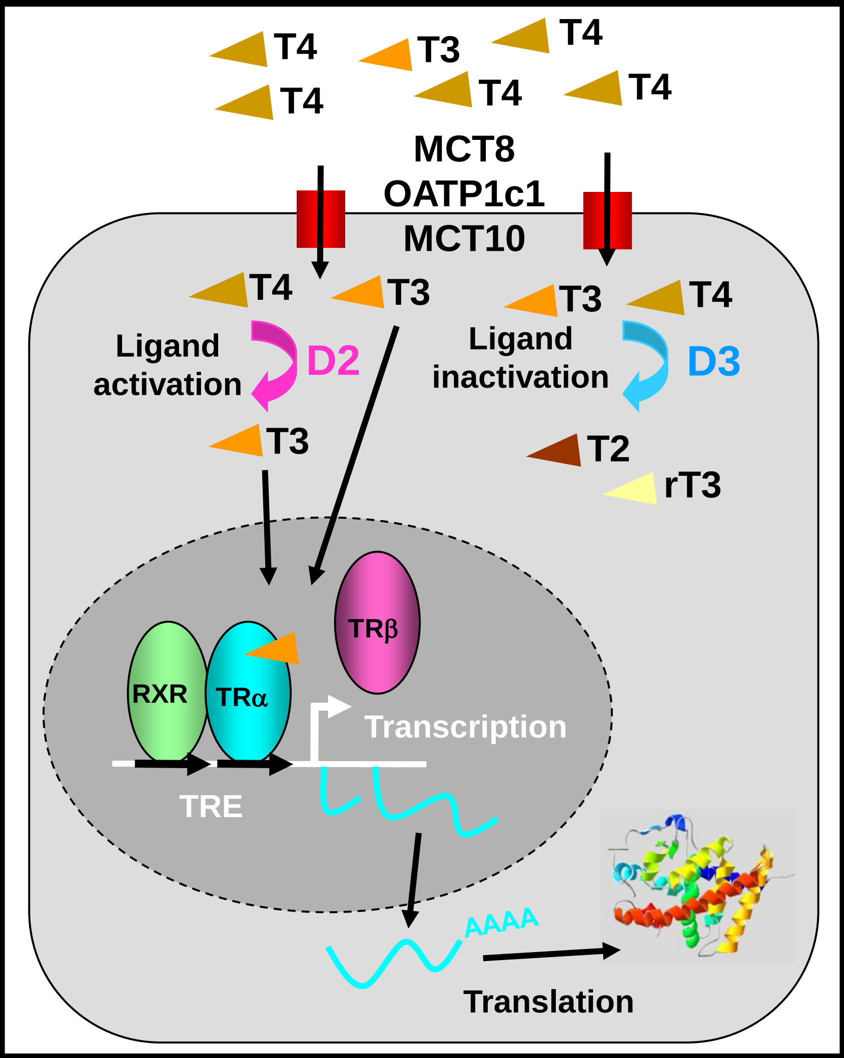
T3/T4 inactivated by 5 deiodination
Type 3 iodothyronine deiodinase

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

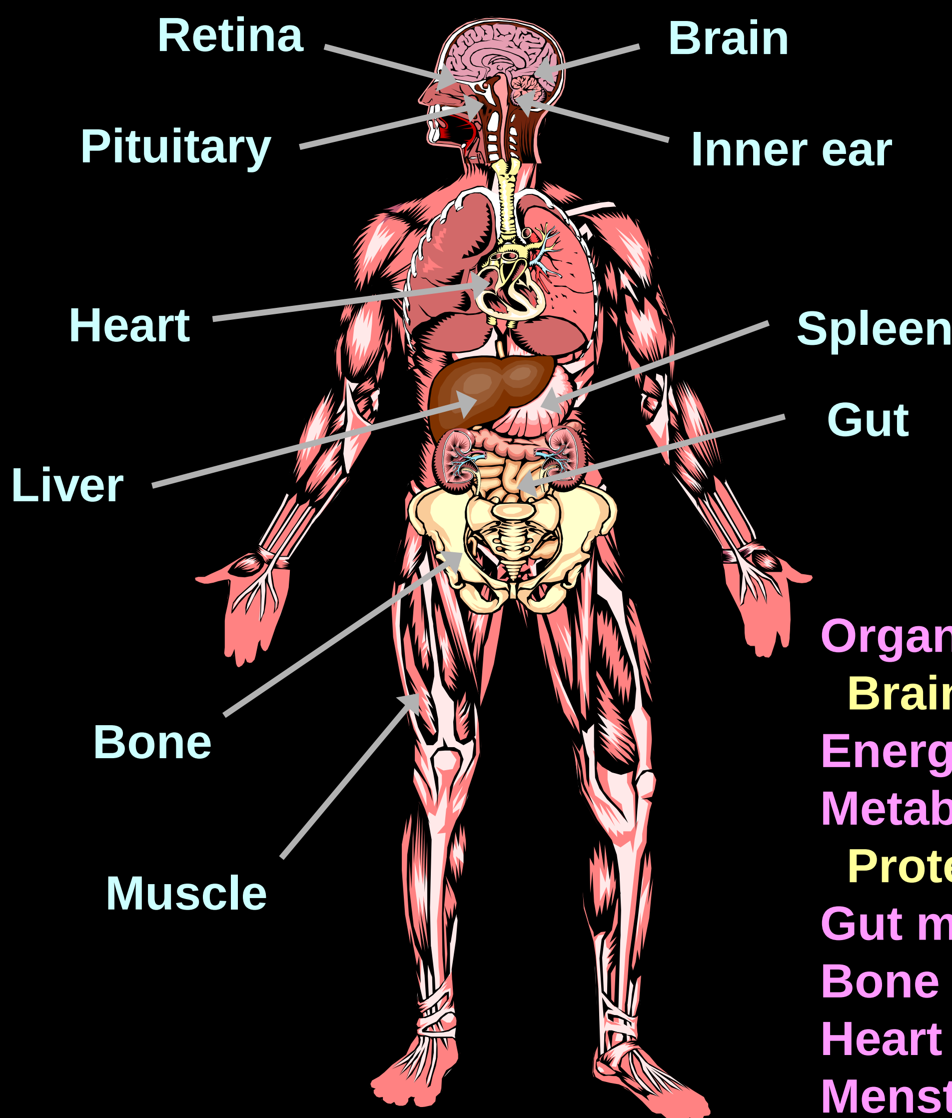
OATP1c1

(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

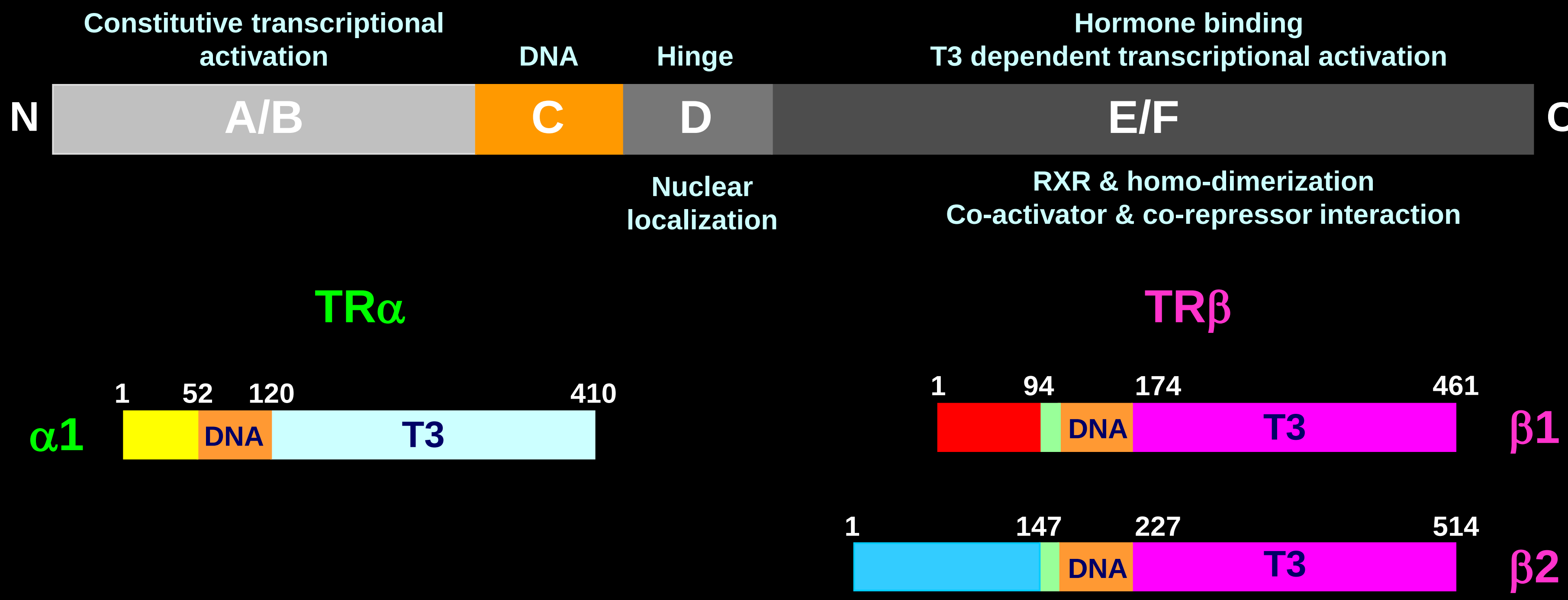
Energy and lipid metabolism
- Increased basal metabolic rate

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

TRs are localized to the nuclear

TRs bind to TREs of varying structure in gene promoters

TRs bind co-repressors, co-activators and other nuclear proteins

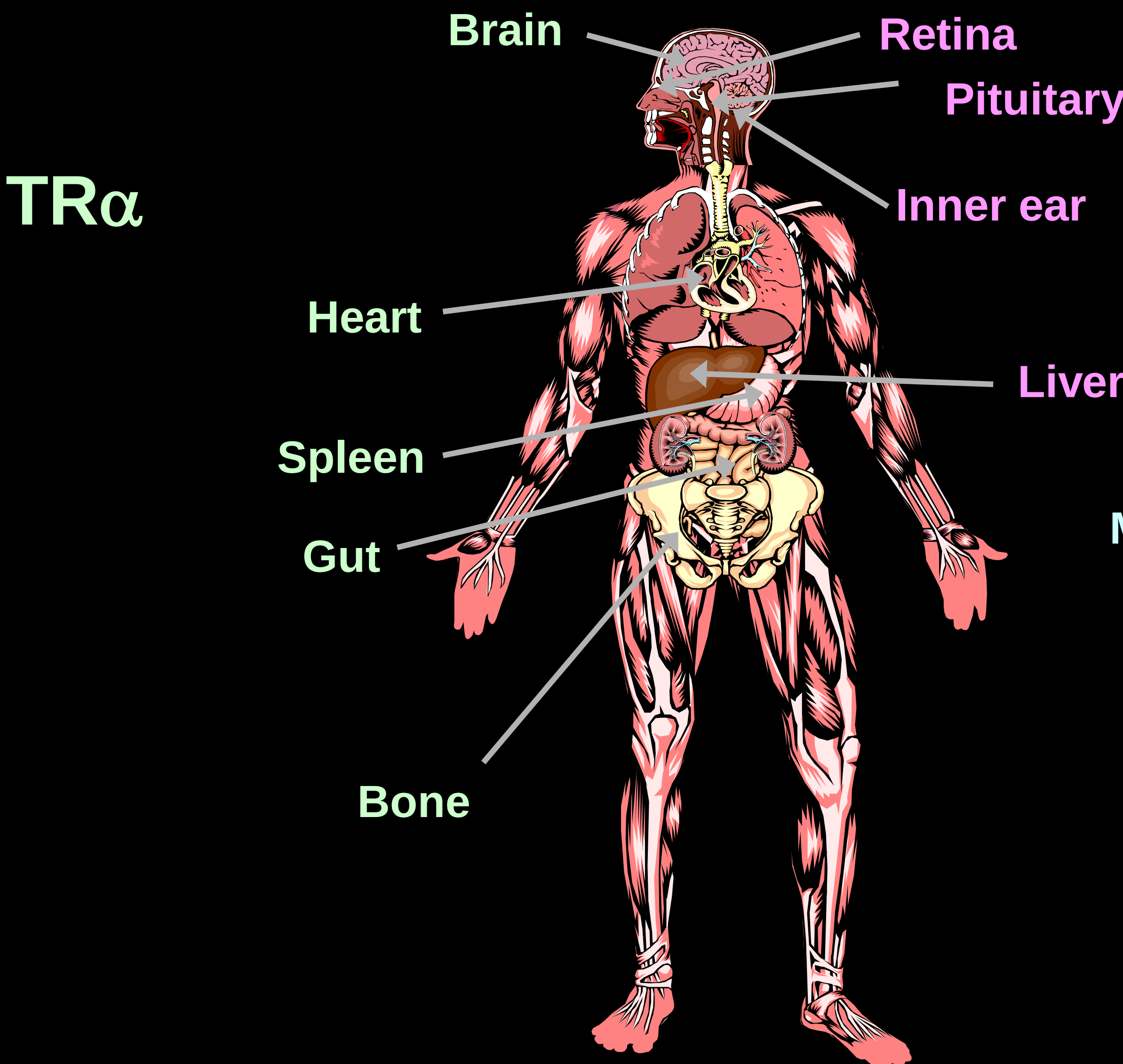
Unliganded apo-TR is a repressor

T3-stimulated positive or negative regulation of T3 target genes

Positive TREs in *GH*, *DIO1*, *ME*, *MHC* genes

Negative TREs in *TRH*, *TSHB* genes

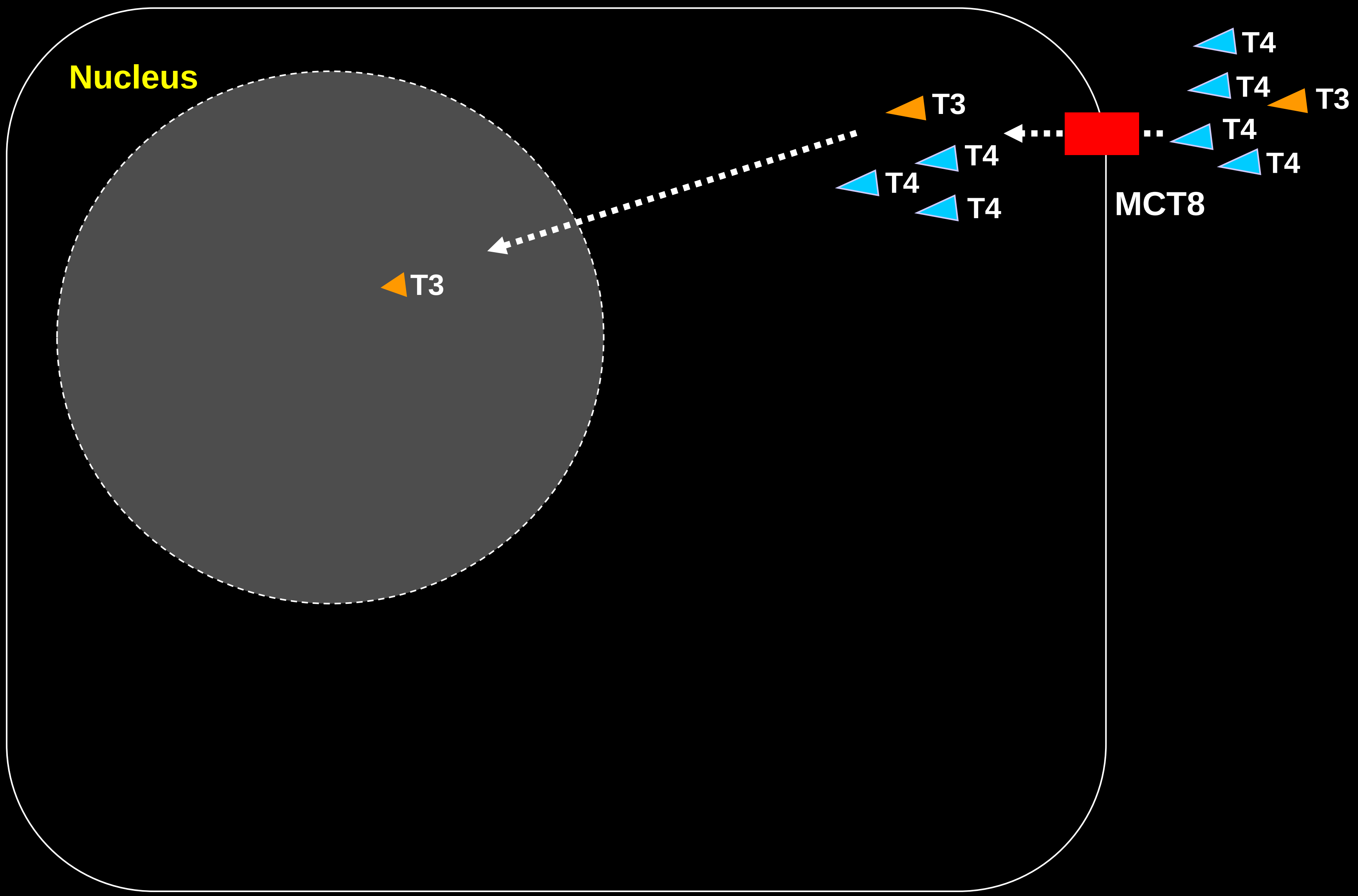
TR isoform-specific target tissues



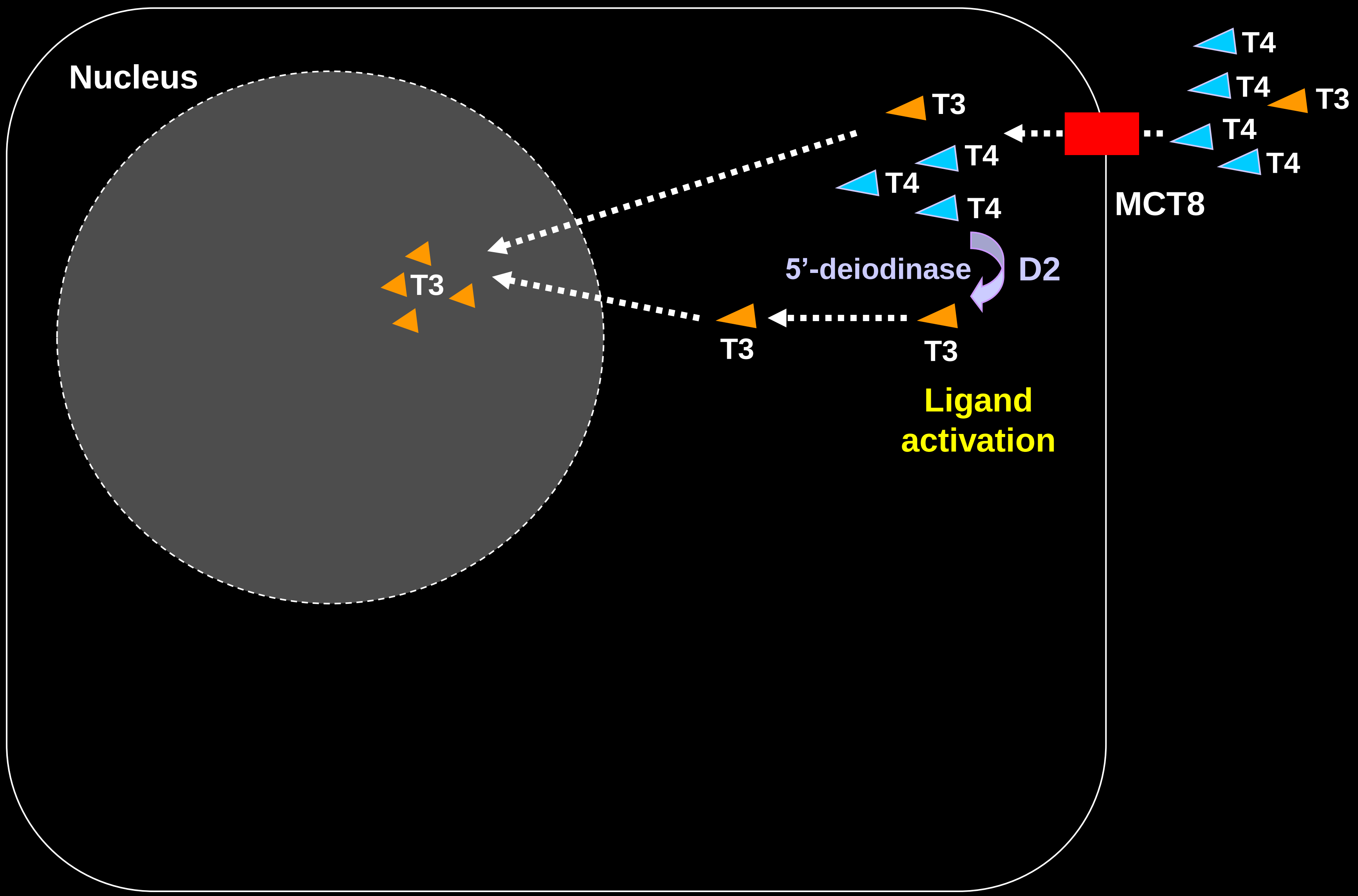
Mixed TRα and TRβ or unknown

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

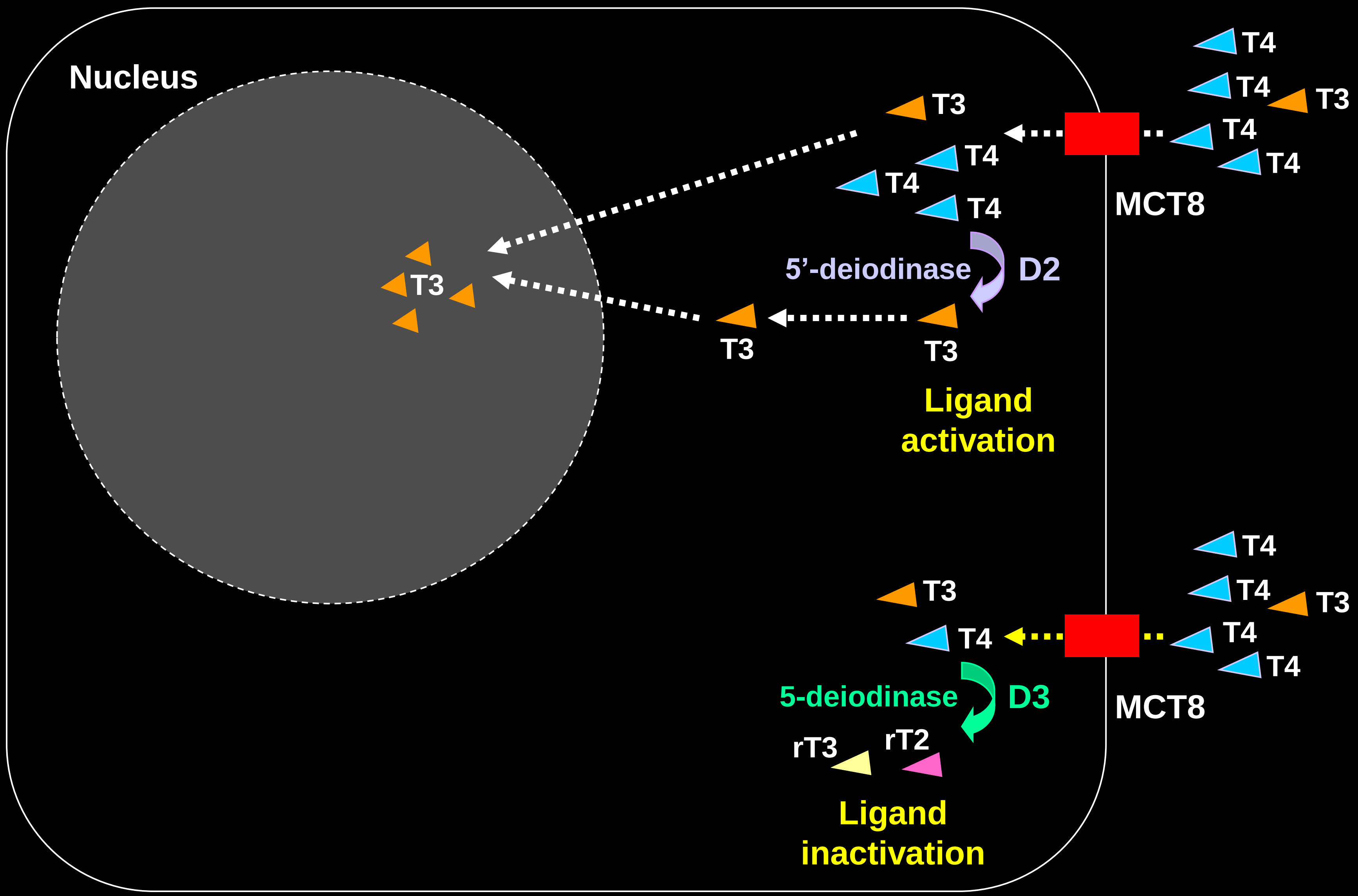
Thyroid hormone action



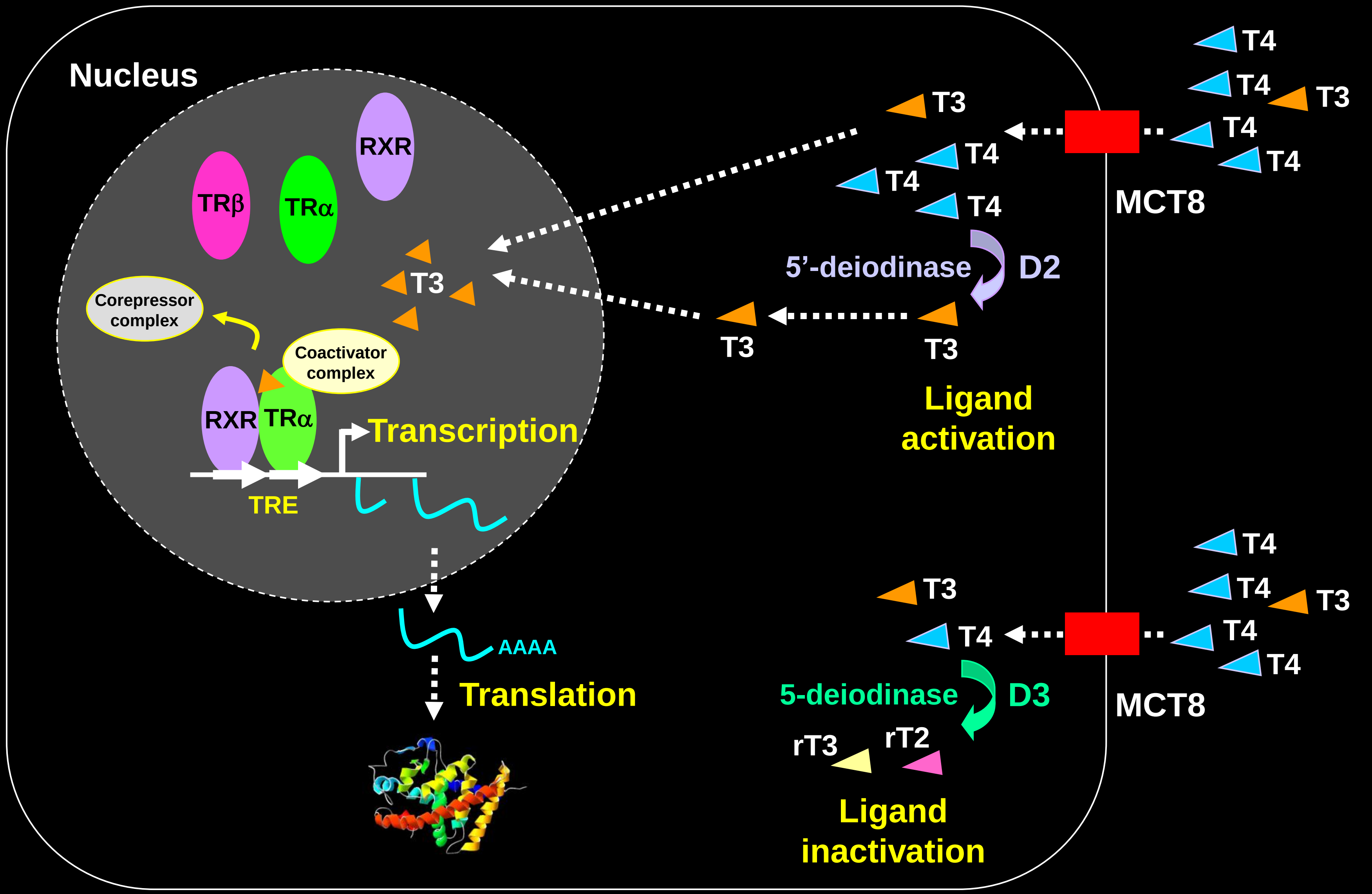
Thyroid hormone action



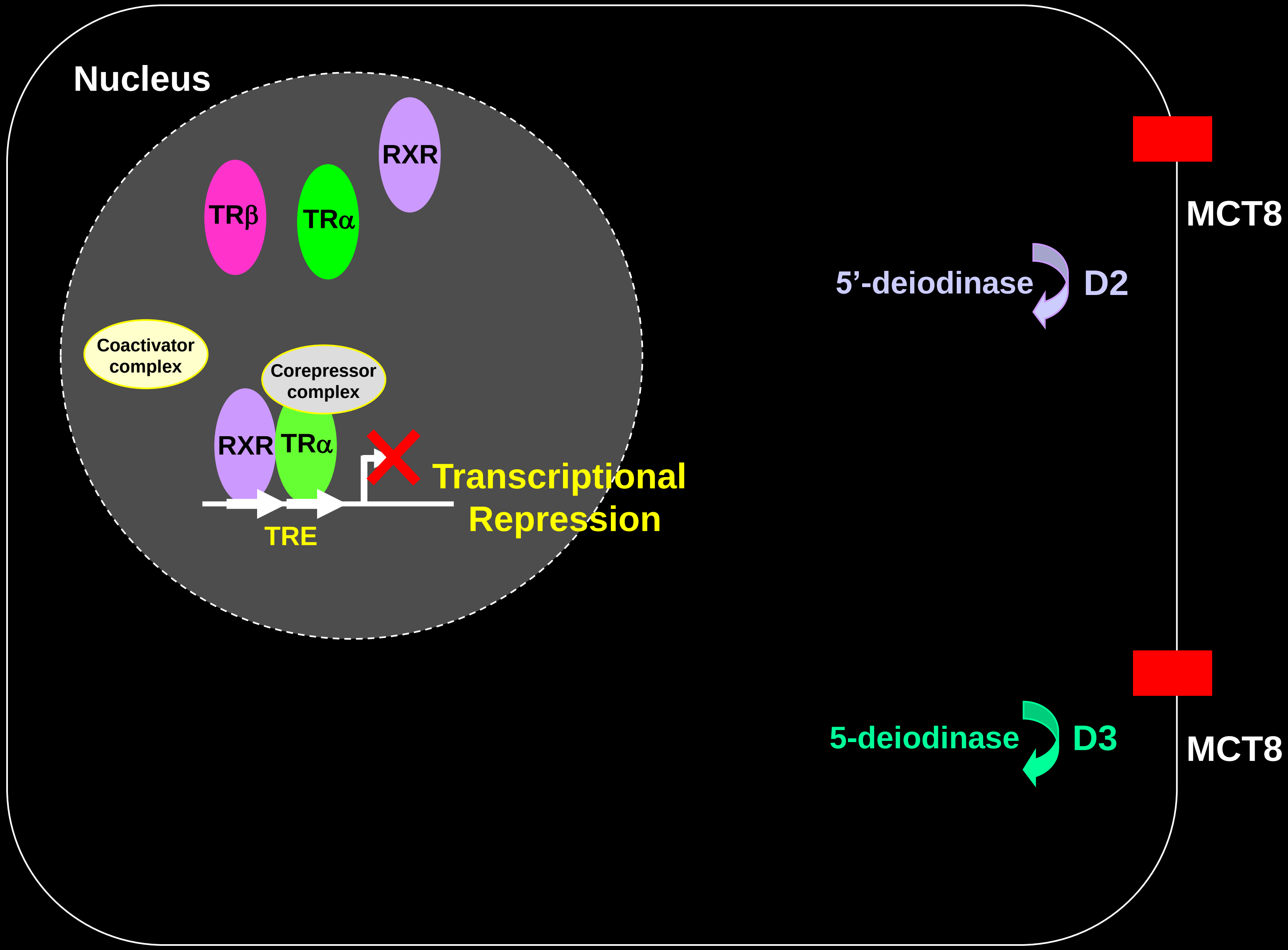
Thyroid hormone action



Thyroid hormone action

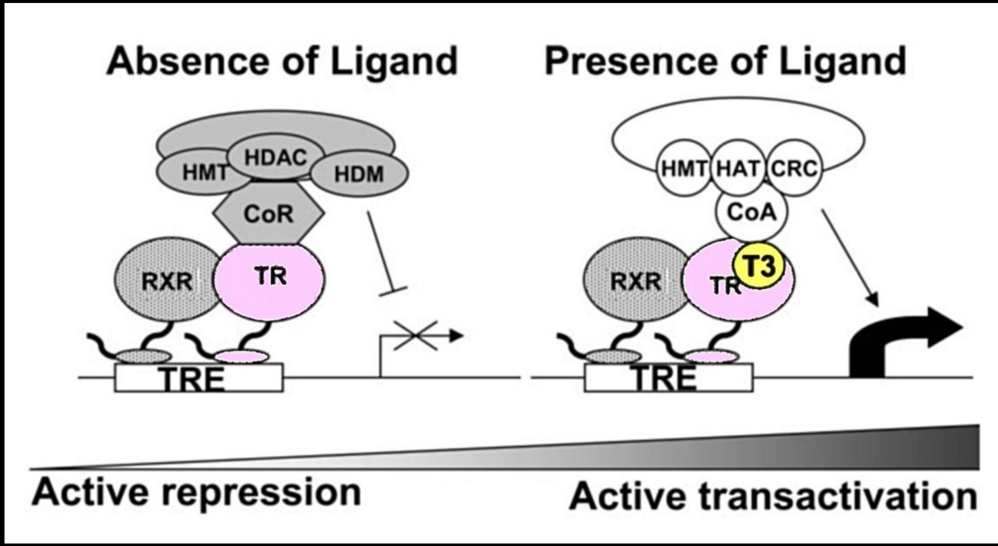


Unliganded apo-TRs are repressors



Regulation of target genes with positive TREs

TR binds to TRE either as homodimer or heterodimer with RXR



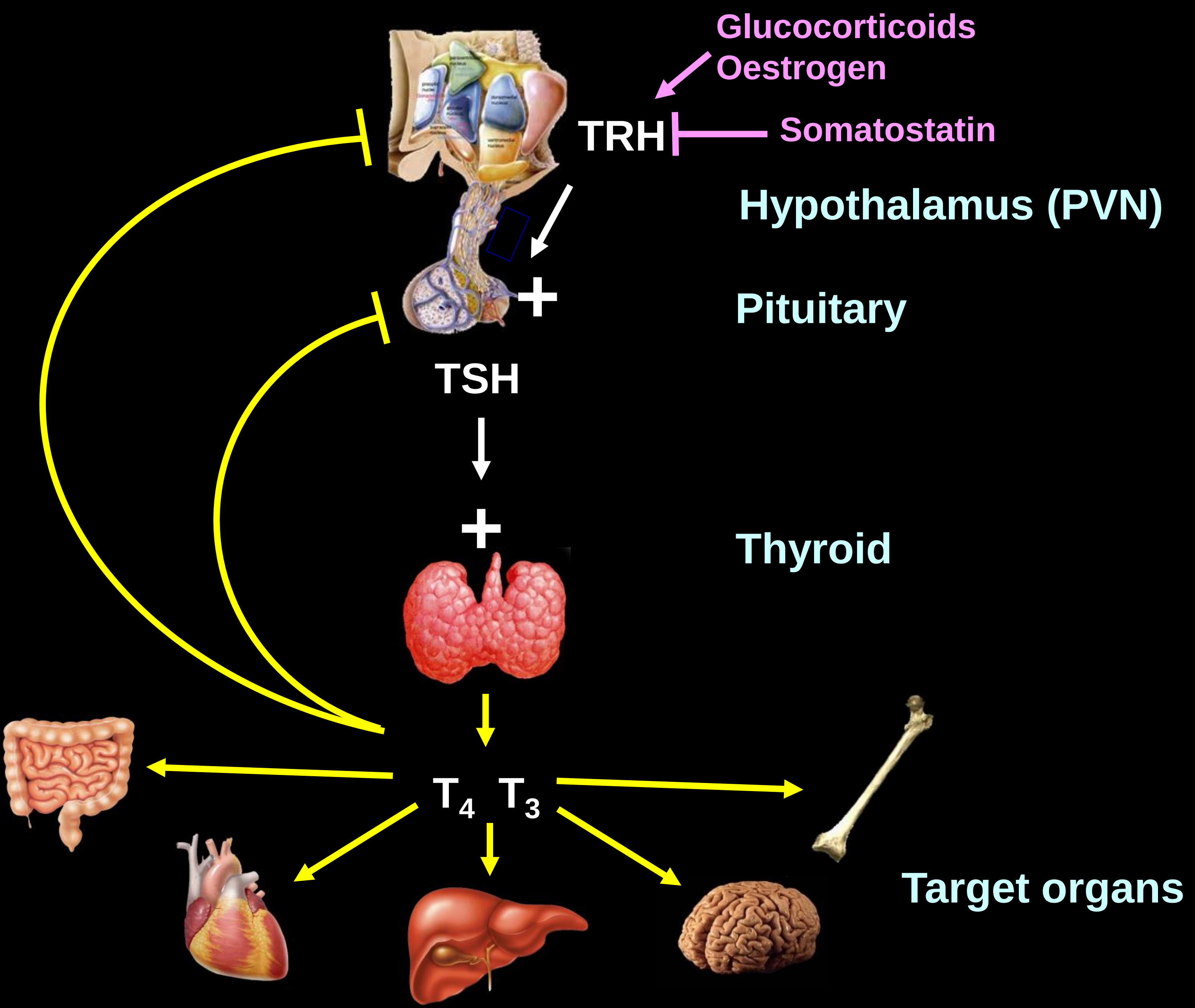
In absence of T3 the TR recruits
- Co-repressor molecules
- Histone methyl transferase, histone deacetylase and histone demethylase
- Interfere with the basal transcription machinery

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

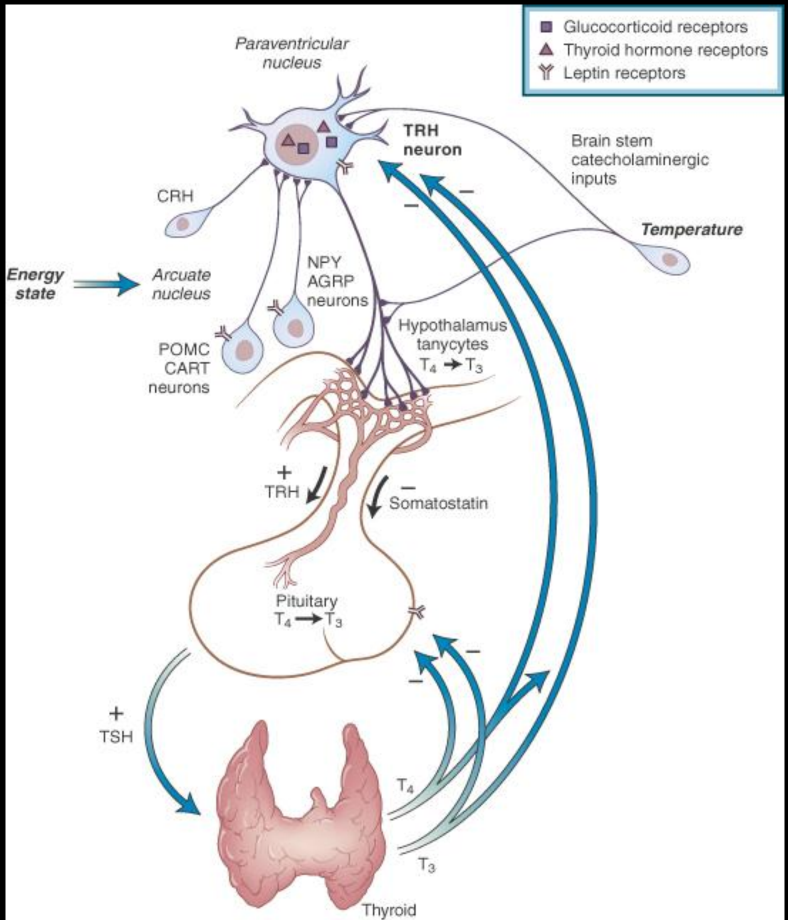


Figure 7–9. Regulation of the hypothalamic-pituitary-thyroid axis. *AGRP*, Agouti-related protein; *CART*, cocaine- and amphetamine-regulated transcript; *CRH*, corticotropin-releasing hormone; *NPY*, neuropeptide Y; *POMC*, proopiomelanocortin; T_3, triiodothyronine; T_4, thyroxine; *TRH*, thyrotropin-releasing 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 “pyroGlu-His-Pro”
- Six copies of Glu-His-Pro in TRH precursor
- 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)

Neural regulation of TRH

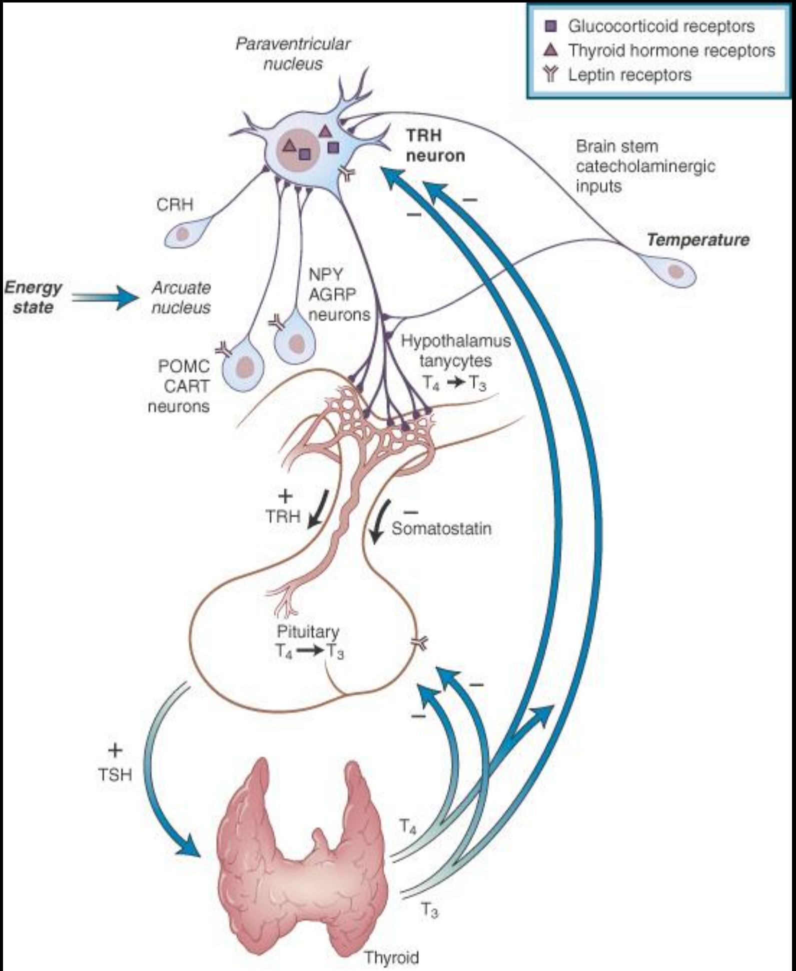


Figure 7–9. Regulation of the hypothalamic-pituitary-thyroid axis. *AGRP*, Agouti-related protein; *CART*, cocaine- and amphetamine-regulated transcript; *CRH*, corticotropin-releasing hormone; *NPY*, neuropeptide Y; *POMC*, proopiomelanocortin; T_3, triiodothyronine; T_4, thyroxine; *TRH*, thyrotropin-releasing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

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

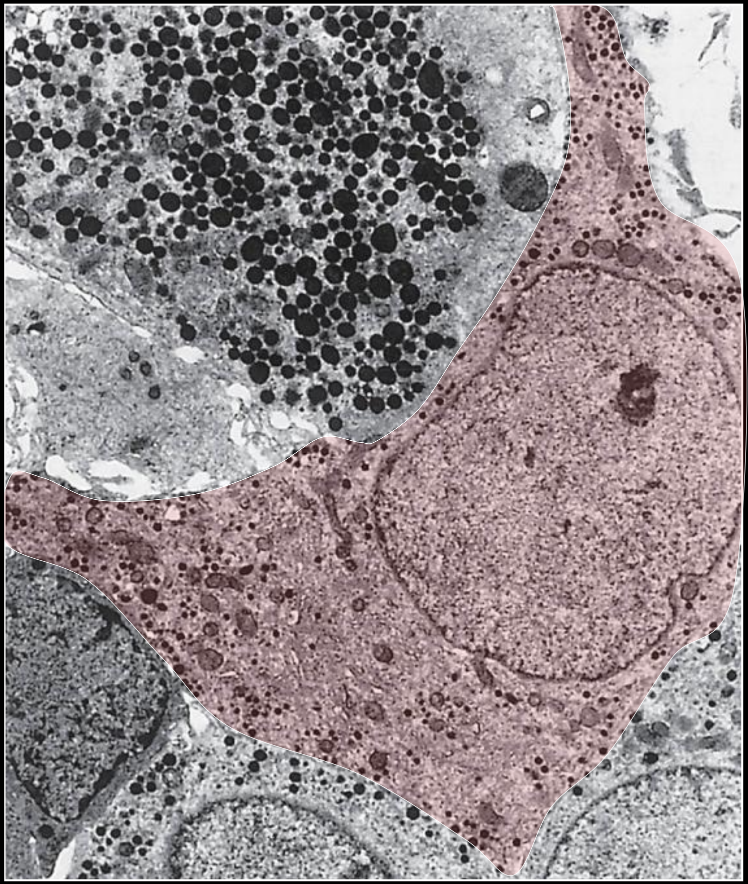
Temperature
Cold exposure increases TSH secretion
(Sympathetic Adr, NA)
Also involves somatostatin, NPY, dopamine and serotonin neurons

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

Sick euthyroid syndrome
Stress
Reduced TRH and thus TSH secretion
Glucorticoids may increase or decrease by direct and indirect actions
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

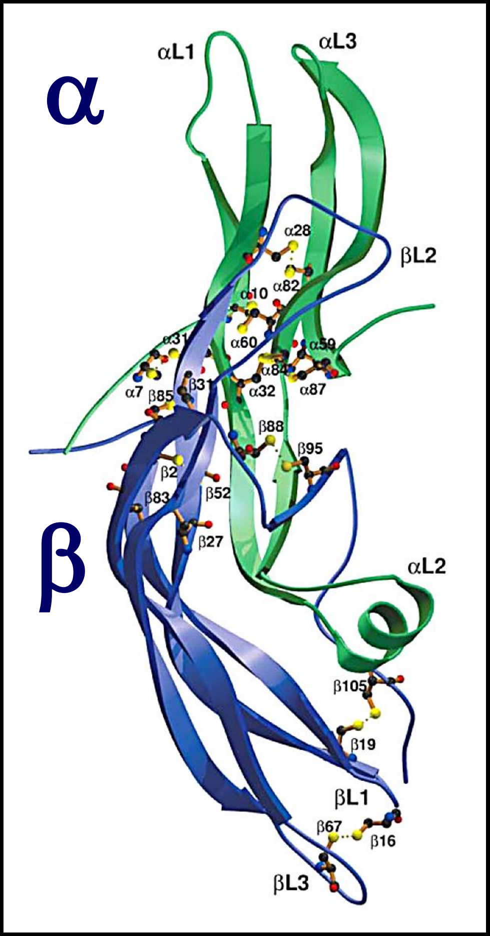
Circadian rhythm

Pulsatile and tonic secretion

Pulses every 3h

Thyroid stimulating hormone (TSH)

Thyrotropin (TSH)



Normal range TSH 0.3-4.2 mU/l

- **100-400IU secreted per day ($T_{1/2}$ 50 minutes)**

Heterodimeric glycoprotein hormone family

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

Thyroid stimulating hormone (TSH)

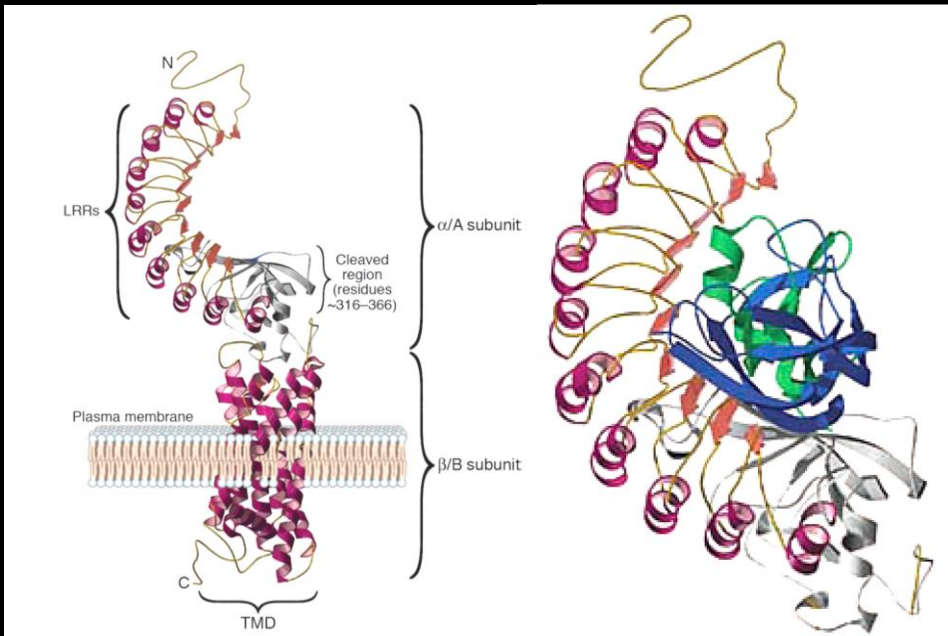
- **Common 42αα α-subunit**
- **Specific β-subunit 41% identity to hCG**
- **intrachain disulphide bonds form cysteine knot motif**

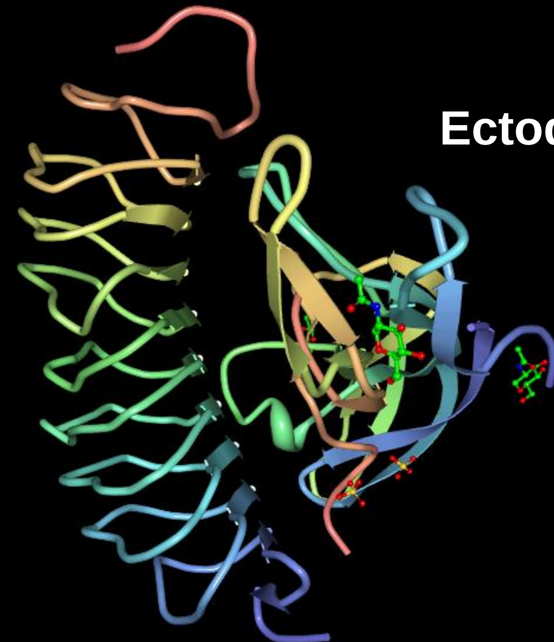
Glycosylation

- **Positively regulated by TRH and negatively by T3/T4**
- **Required for normal folding and potency**
- **Determines rate of TSH 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**

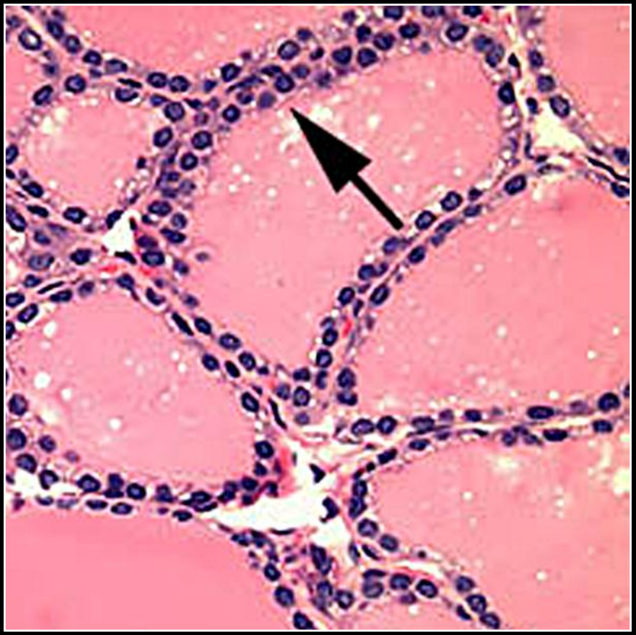
Cystein rich flanking hinge region

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

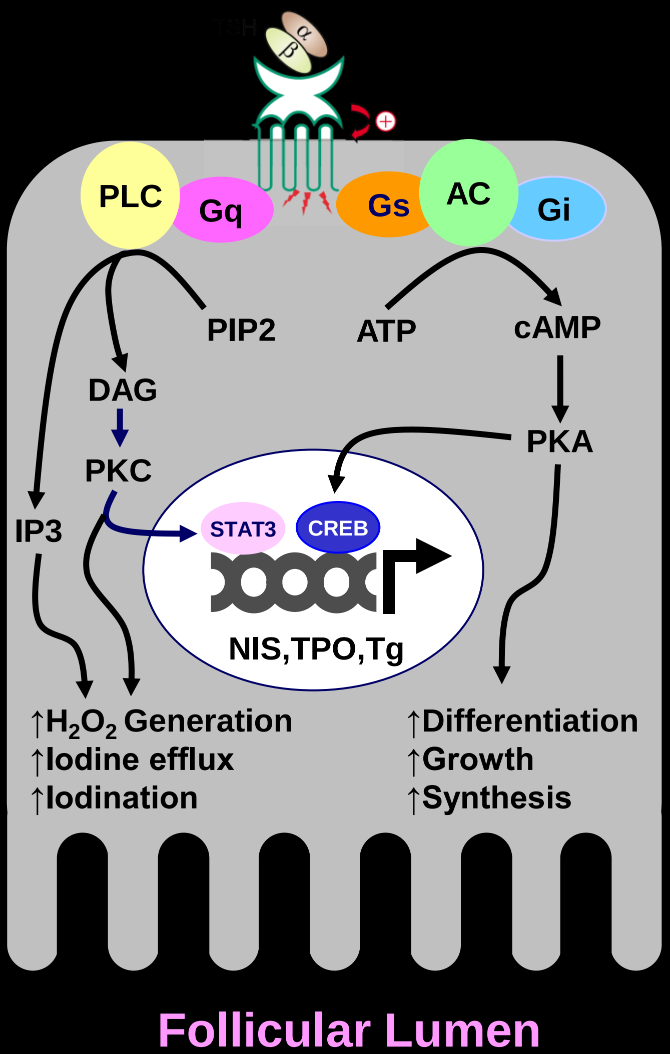
Follicular cell proliferation and differentiation

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

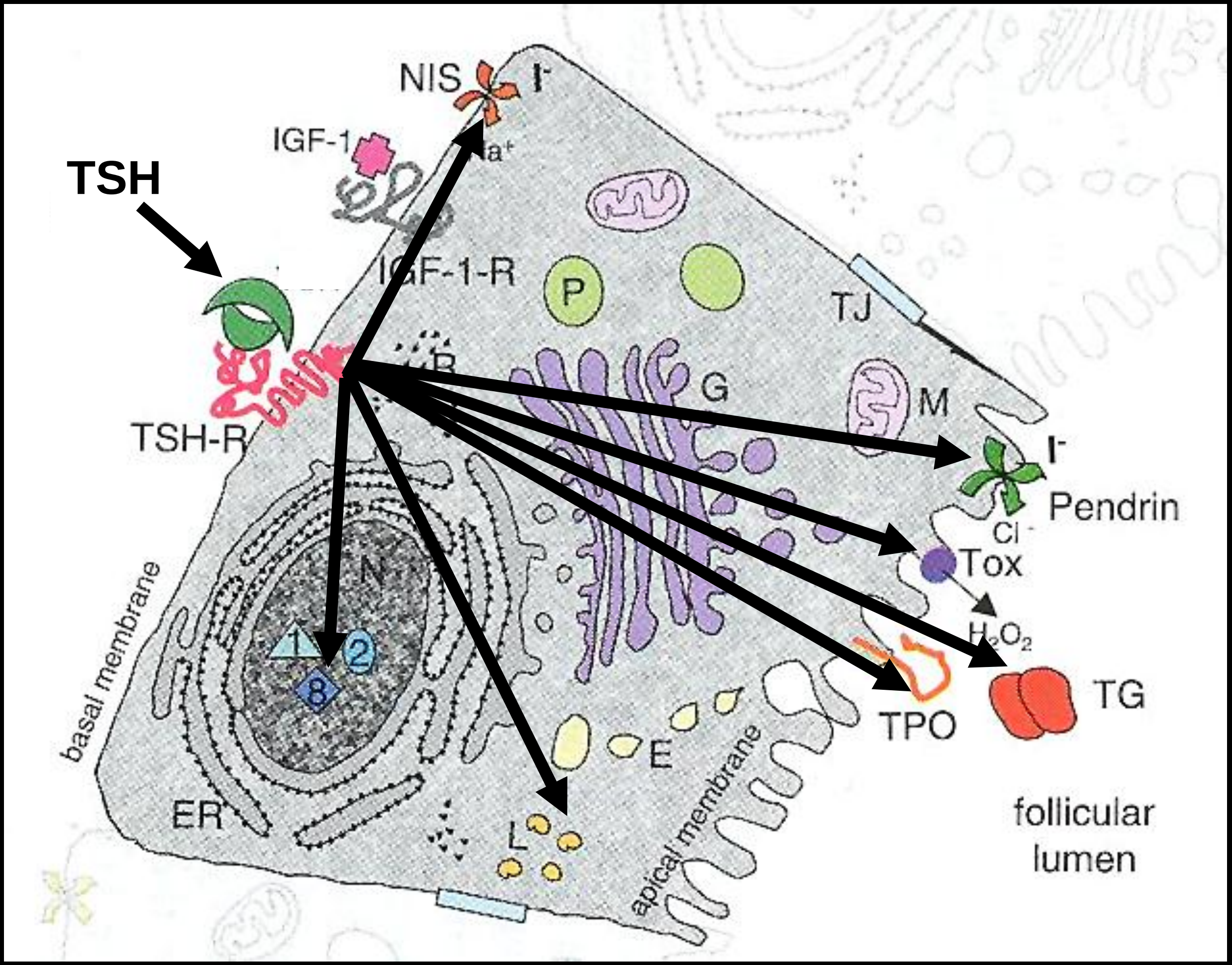


$G\alpha_s$/AC/cAMP/PKA regulates
- Sodium-iodide symporter (NIS)
- Pendren membrane localisation
- Thyroid peroxidase (TPO)
- Thyroglobulin (Tg)

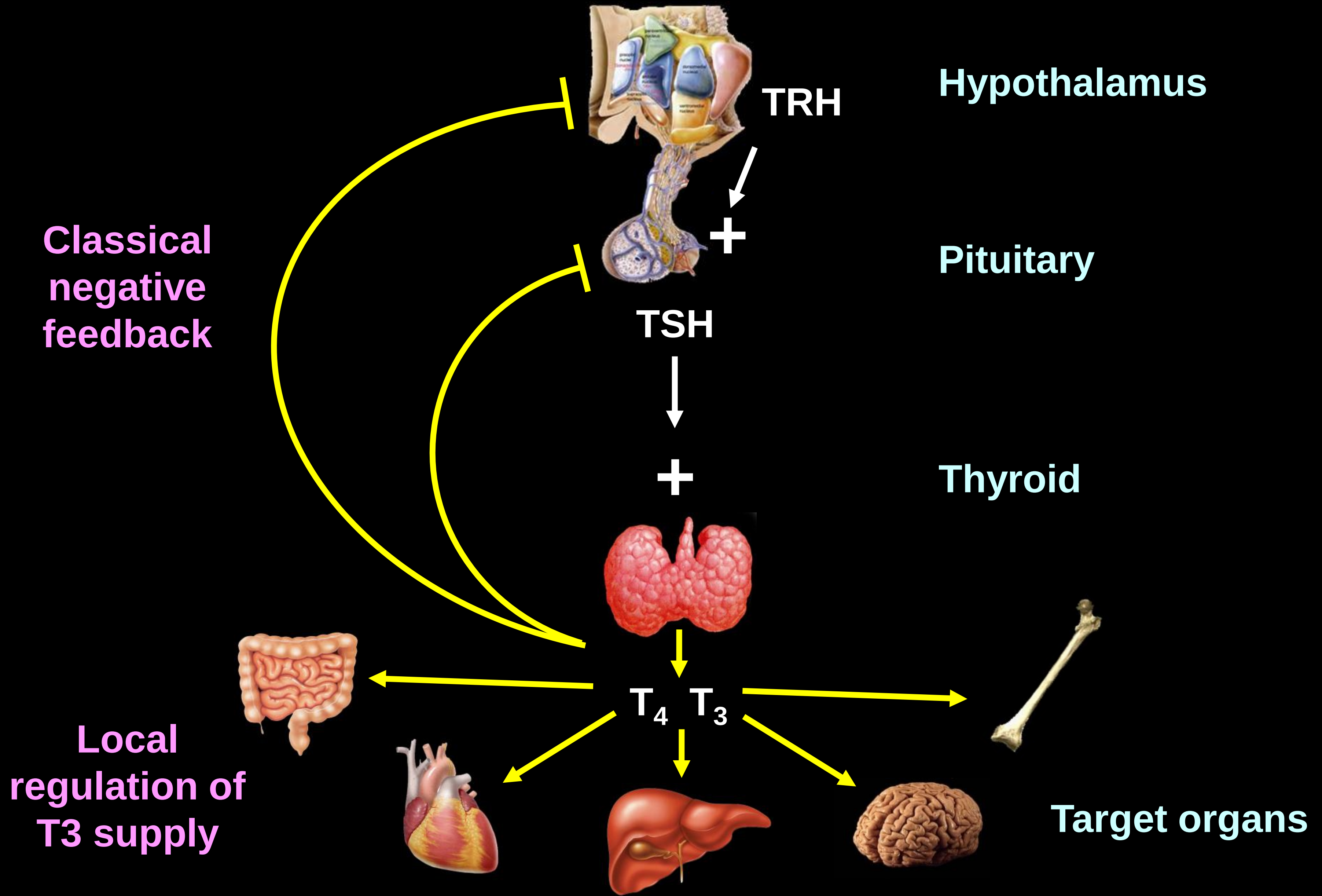
$G\alpha_q$/PLC/PKC/Ca^{2+} regulates
- Thyroglobulin iodination
- H_2O_2 generation (Duox)

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
Section III Williams Textbook of Endocrinology 11th Edition 297-411
(Editors Kronenberg HM, Melmed S, Polonsky KS and Larsen PR (Saunders)

Thyroid hormone action
Yen PM (2001) Physiological and Molecular Basis of Thyroid Hormone Action.
***Physiol Rev* 81:1097–1142**

The iodothyronine deiodinases
Antonio C. Bianco AC (2006) Deiodinases: implications of the local control of thyroid hormone action. *J. Clin. Invest.* 116:2571–2579.

TSH and TSHR
Davies TF et al. (2005) Thyrotropin receptor–associated diseases:from adenomata to Graves disease. *J. Clin. Invest.* 115:1972–1983

Learning objectives

1. Describe the development of the thyroid
2. Describe anatomy of the thyroid and the structure of a follicle
3. List hormones produced by the thyroid.
4. Describe principal features of thyroid hormone synthesis, storage, release
5. Describe the physiological actions of thyroid hormone
6. Explain the mechanism of action of thyroid hormone
7. Describe regulation of thyroid status by the hypothalamus-pituitary-thyroidal axis.
8. Describe the role of deiodinases in regulation of systemic thyroid hormone concentration and local thyroid hormone action.
9. Contrast the mechanism of action of TSH and T3