

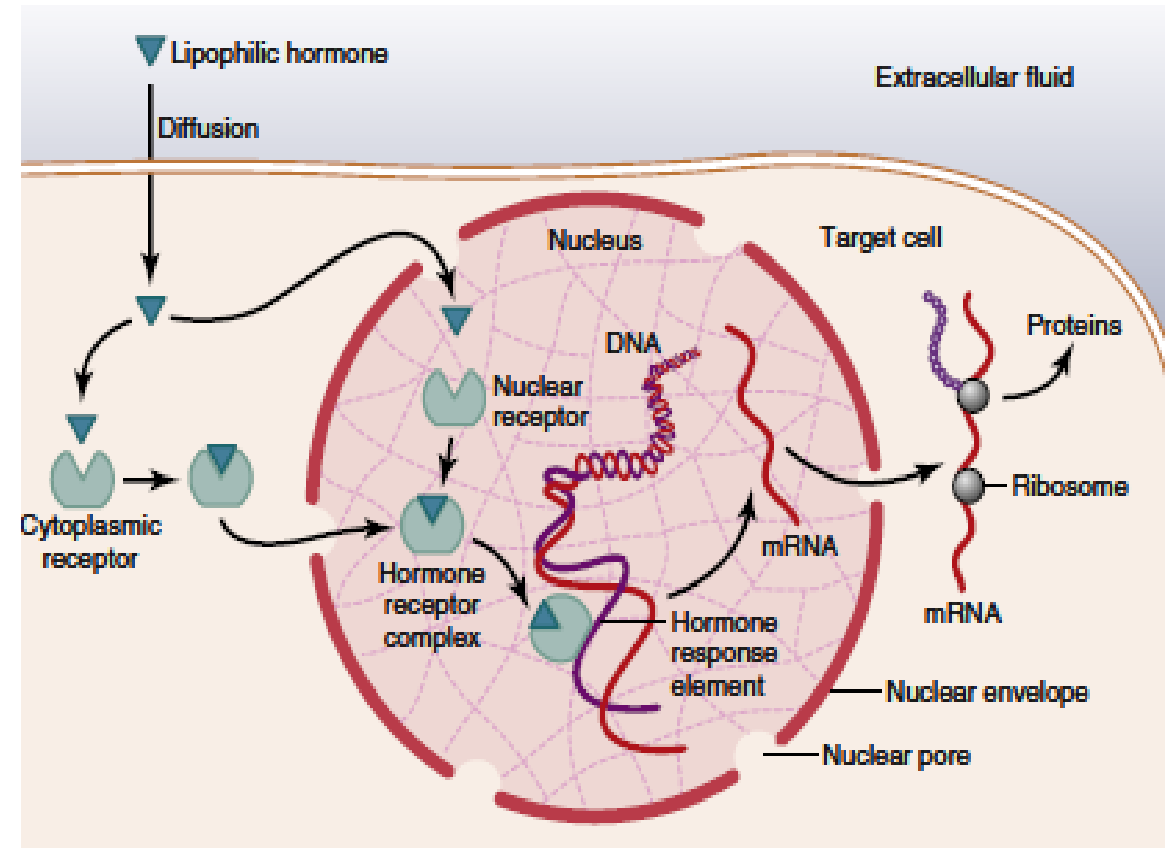
Signal Transduction Lec 4

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HORMONES THAT ACT MAINLY ON THE GENETIC MACHINERY OF THE CELL

Steroid Hormones and Thyroid Hormones

- 1. Lipophilic hormone diffuses across the cell membrane and enters the cytoplasm of the cell, where it binds with a specific *receptor protein* (either *cytoplasmic* or *nuclear*).
- 2. The combined receptor protein–hormone then diffuses into or is transported into the nucleus.
- 3. The combination binds at specific points on the DNA strands in the chromosomes, which forms **hormone response element (HRE)** activates the transcription process of specific genes to form mRNA.
- 4. The mRNA diffuses into the cytoplasm, where it promotes the translation process at the ribosomes to form new proteins.

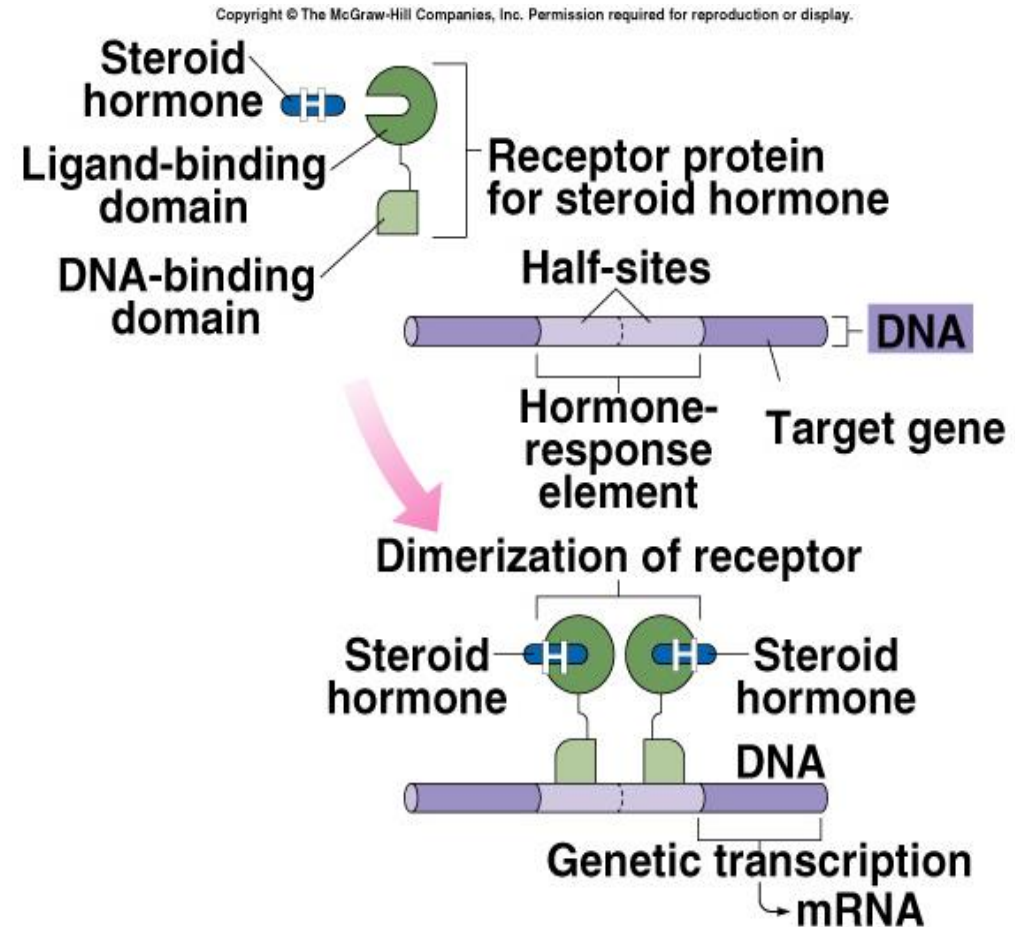


Lipophilic Hormone Receptors

- Steroid receptors are located in cytoplasm and in the nucleus.
- Function within cell to activate genetic transcription.
 - Messenger RNA directs synthesis of specific enzyme proteins that change metabolism.
- Each nuclear hormone receptor has 2 regions:
 - A ligand (hormone)-binding domain.
 - DNA-binding domain.
- Receptor must be activated by binding to hormone before binding to specific region of DNA called HRE (hormone responsive element).
- Binding of the hormone receptor complex with DNA “turns on” or activates a specific gene within the target cell . This gene contains a code for synthesizing a given protein.
- The new mRNA leaves the nucleus and enters the cytoplasm, where it binds to a ribosome, the “workbench” that mediates the assembly of new proteins.

Mechanisms of Steroid Hormone Action

- Cytoplasmic receptor binds to steroid hormone.
- Translocate to nucleus.
- DNA-binding domain binds to specific HRE of the DNA.
- Dimerization occurs.
 - Process of 2 receptor units coming together at the 2 half-sites.
- Stimulates transcription of particular genes.

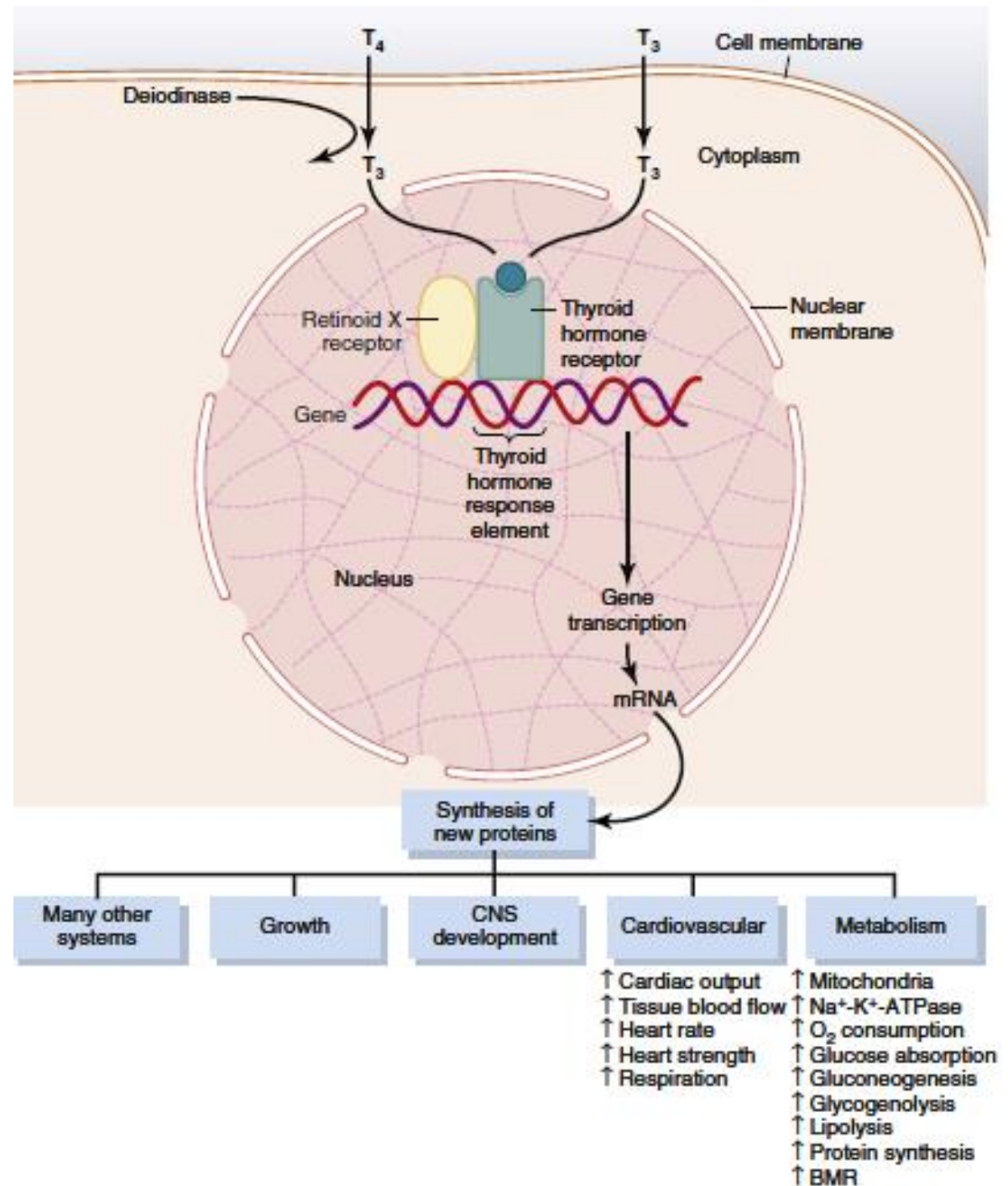


Thyroid Hormones Increase Gene Transcription in the Cell Nucleus

- The thyroid hormones *thyroxine* and *triiodothyronine* cause increased transcription by specific genes in the nucleus
- First bind directly with receptor proteins in the nucleus,
- These receptors are *activated transcription factors* located within the chromosomal complex, and they control the function of the gene promoters
- 1. They activate the genetic mechanisms for synthesizing many types of intracellular proteins—probably 100 or more. Many of these intracellular proteins are enzymes that promote enhanced intracellular metabolic activity in virtually all cells of the body.
- 2. Once bound to the intranuclear receptors, the thyroid hormones can continue to express their control functions for days or even weeks.

Thyroid Hormone

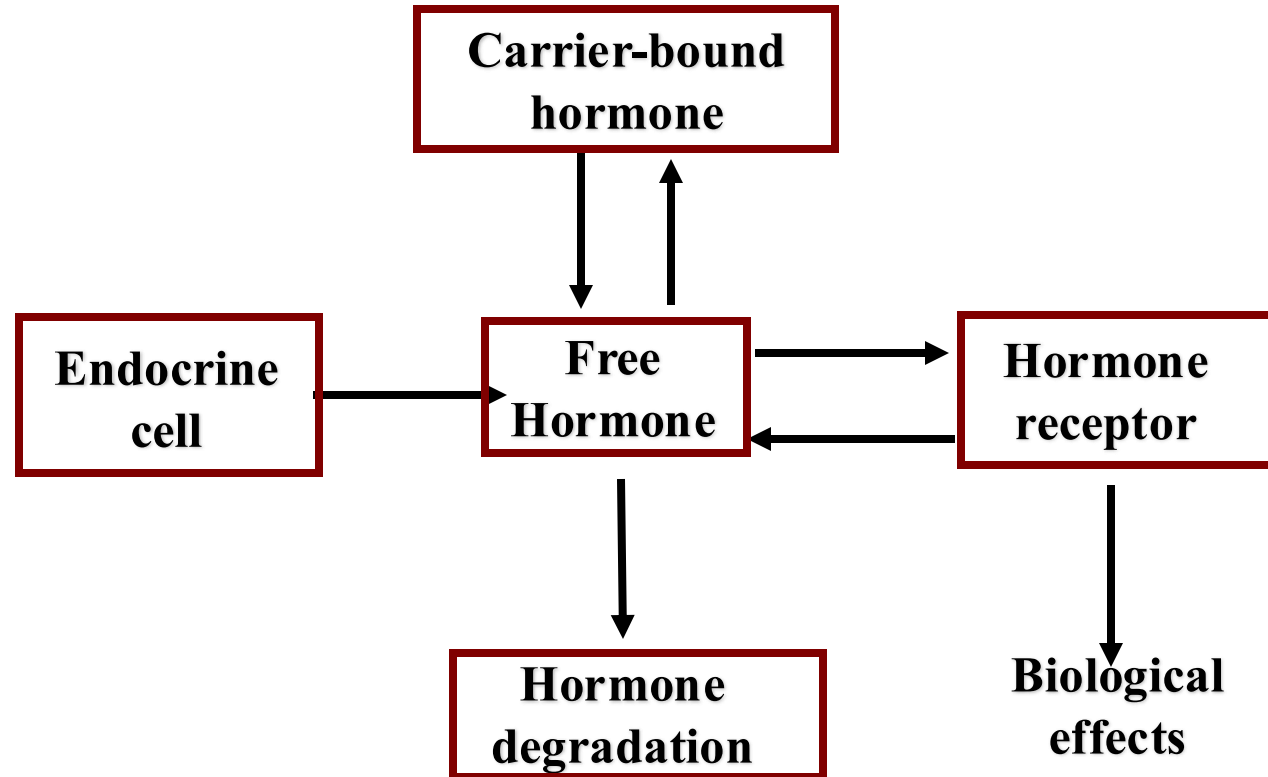
- T_4 passes into cytoplasm and is converted to T_3 .
- Receptor proteins located in nucleus.
 - T_3 binds to ligand-binding domain.
 - Other half-site is vitamin A derivative (9-cis-retinoic) acid.
 - DNA-binding domain can then bind to the half-site of the HRE.
 - Two partners can bind to the DNA to activate HRE.
 - Stimulate transcription of genes.



Steroid Hormone Signaling

- Most steroid actions are accomplished by hormonal binding with intracellular receptors that leads to gene activation
- This mechanism is considered slow because it is working on gene expression
- Recent studies have unveiled another mechanism by which steroid hormones induce effects that occur too rapidly
- Some steroid hormones, most notably some of the sex hormones, bind with unique steroid receptors in the plasma membrane, in addition to binding with the traditional steroid receptors in the nucleus.
- This membrane binding leads to **nongenomic steroid receptor actions**, actions accomplished by something other than altering gene activity
- May work by inducing changes in ionic flux across the membrane or by altering activity of cellular enzymes.

Determinants of Free Hormone Receptor Binding



Correlation of Plasma Half-Life & Metabolic Clearance of Hormones with Degree of Protein Binding

Hormone	Protein binding (%)	Plasma half-life	Metabolic clearance (ml/minute)
Thyroid			
Thyroxine	99.97	6 days	0.7
Triiodothyronine	99.7	1 day	18
Steroids			
Cortisol	94	100 min	140
Testosterone	89	85 min	860
Aldosterone	15	25 min	1100
Proteins			
Thyrotropin TSH	little	50 min	50
Insulin	little	8 min	800
Antidiuretic hormone	little	8 min	600

Circulating Transport Proteins

Transport Protein	Principle Hormone Transported
Specific	
Corticosteroid binding globulin (CBG, transcortin)	Cortisol, aldosterone
Thyroxine binding globulin (TBG)	Thyroxine, triiodothyronine
Sex hormone-binding globulin (SHBG)	Testosterone, estrogen
Nonspecific	
Albumin	Most steroids, thyroxine, triiodothyronine
Transthyretin (prealbumin)	Thyroxine, some steroids

Signaling molecule
(hormones)



Receptor of target cell



Intracellular molecule
(second messengers)



Biological effect



**Signal
transduction**

Thank You & Good Luck