



Cell Communication III: Steroid Hormones

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Cell Communication Review

- Small Molecules
 - Example
 - What are its chemical characteristics?
- Peptides and Proteins
 - Example hormone?
 - Characteristics of this peptide hormone?





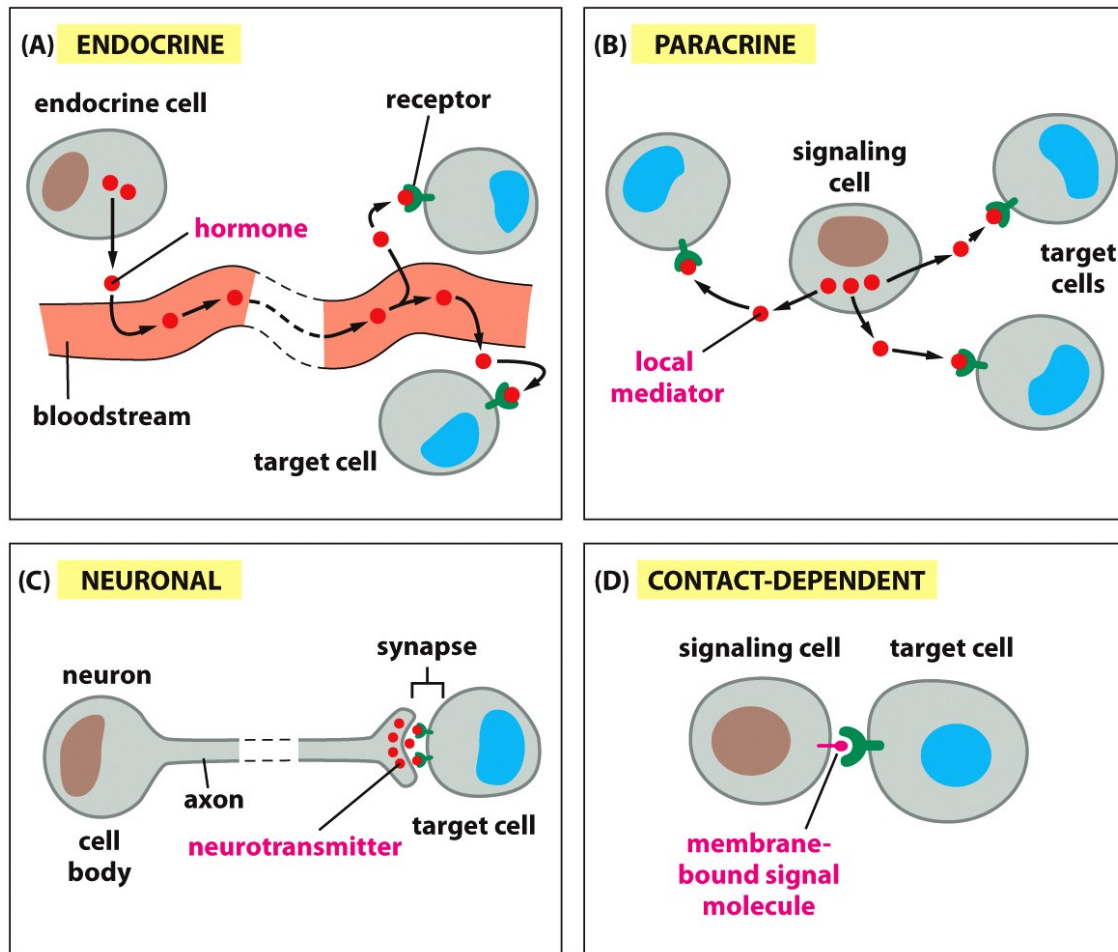
Cell Communication Review

- Small Molecules
 - Example Ca^{2+}
 - What are its chemical characteristics?
- Peptides and Proteins
 - Example hormone?
 - Characteristics of this peptide hormone?



Cell Communication Review II


- How do these signals get around?



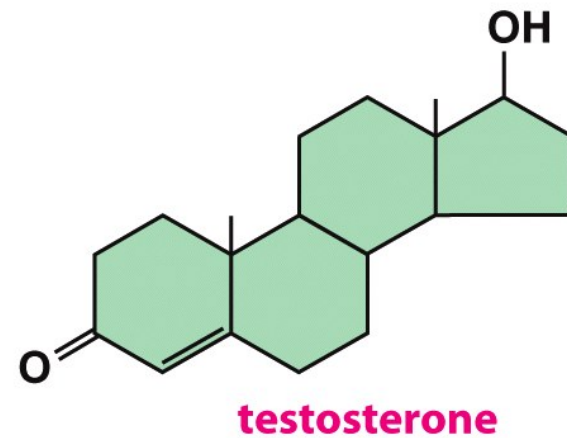
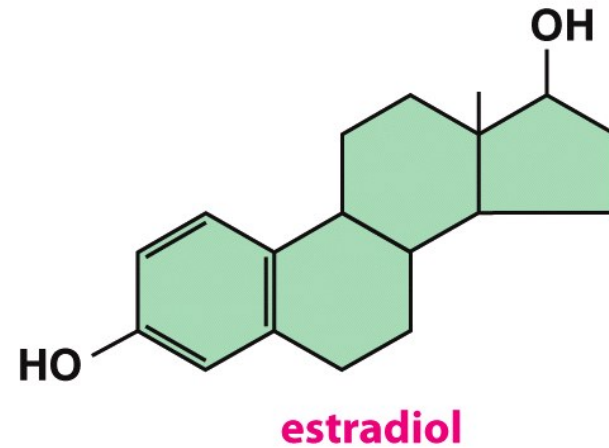
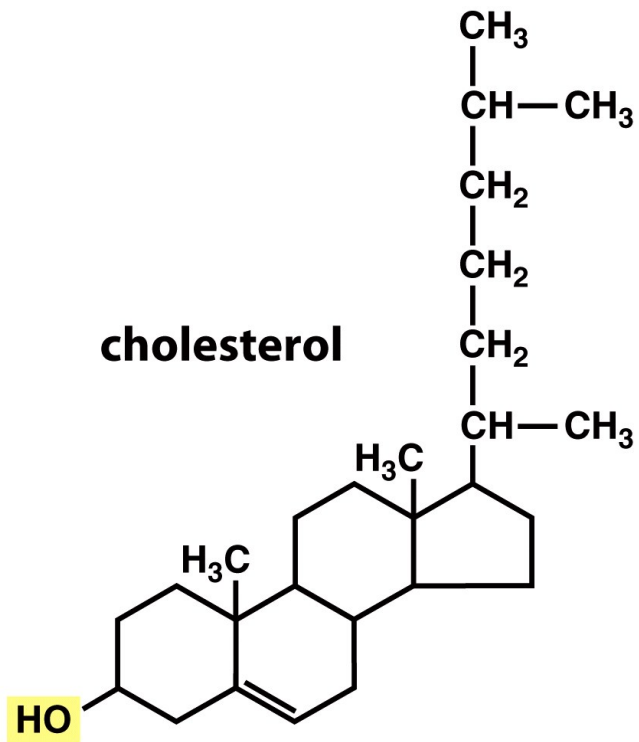


Steroid Hormones

- Different class of hormone
 - Structure
 - Transport
 - Receptors
 - Function

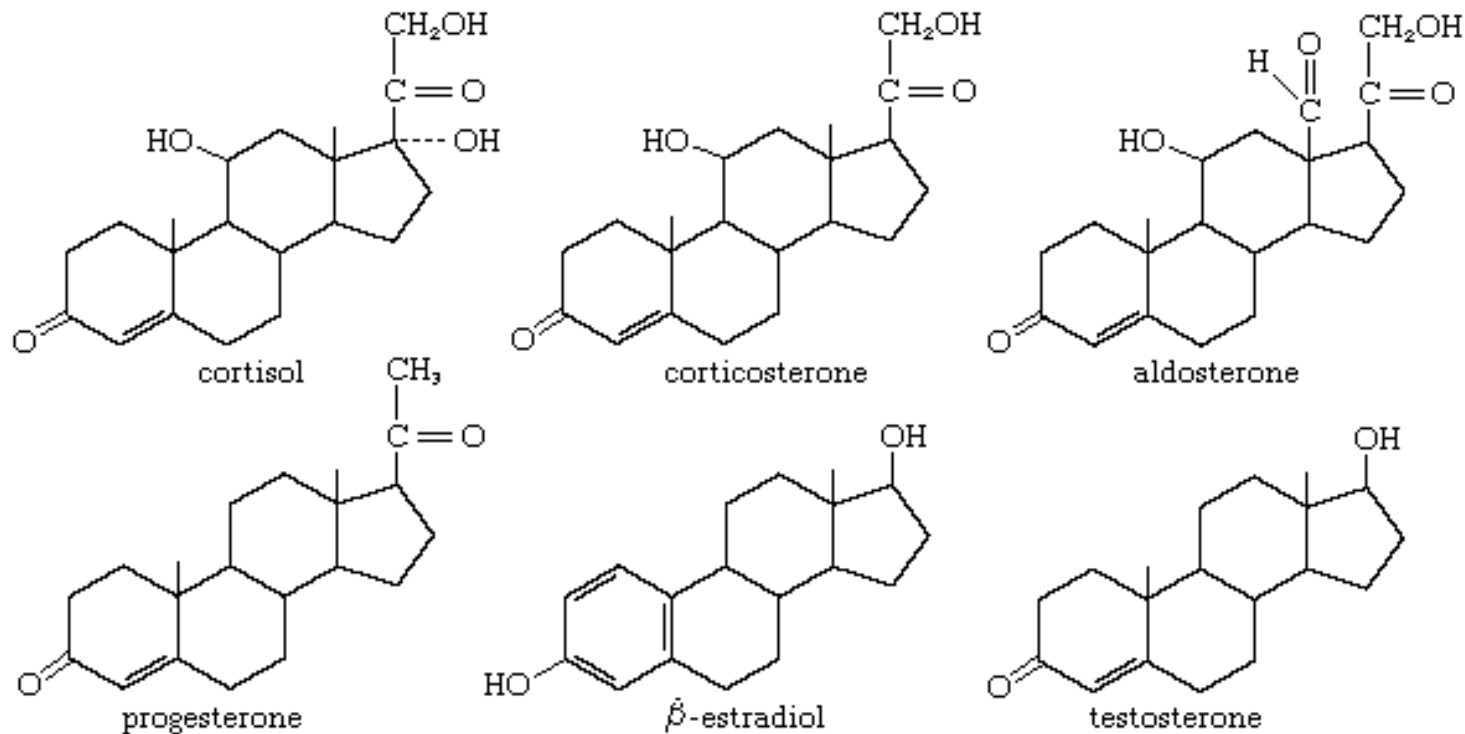
 - Estrogen will be the model steroid hormone for this lecture
 - Contrast to Insulin, our model peptide hormone
- 

Derived from Cholesterol



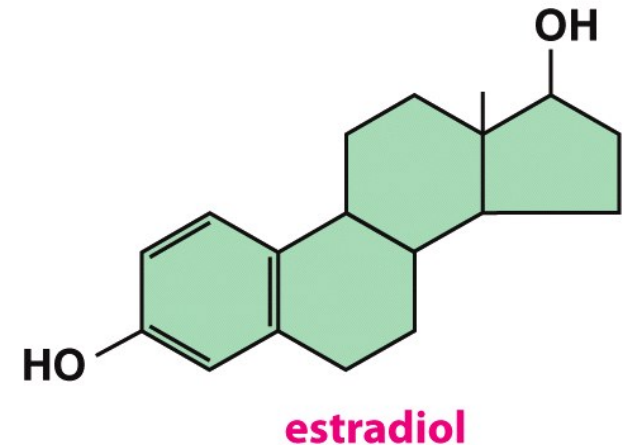
Steroid Hormones

- Generally:
 - Considered small molecules
 - Very similar chemical structures
 - Mostly non-polar bonds → hydrophobic

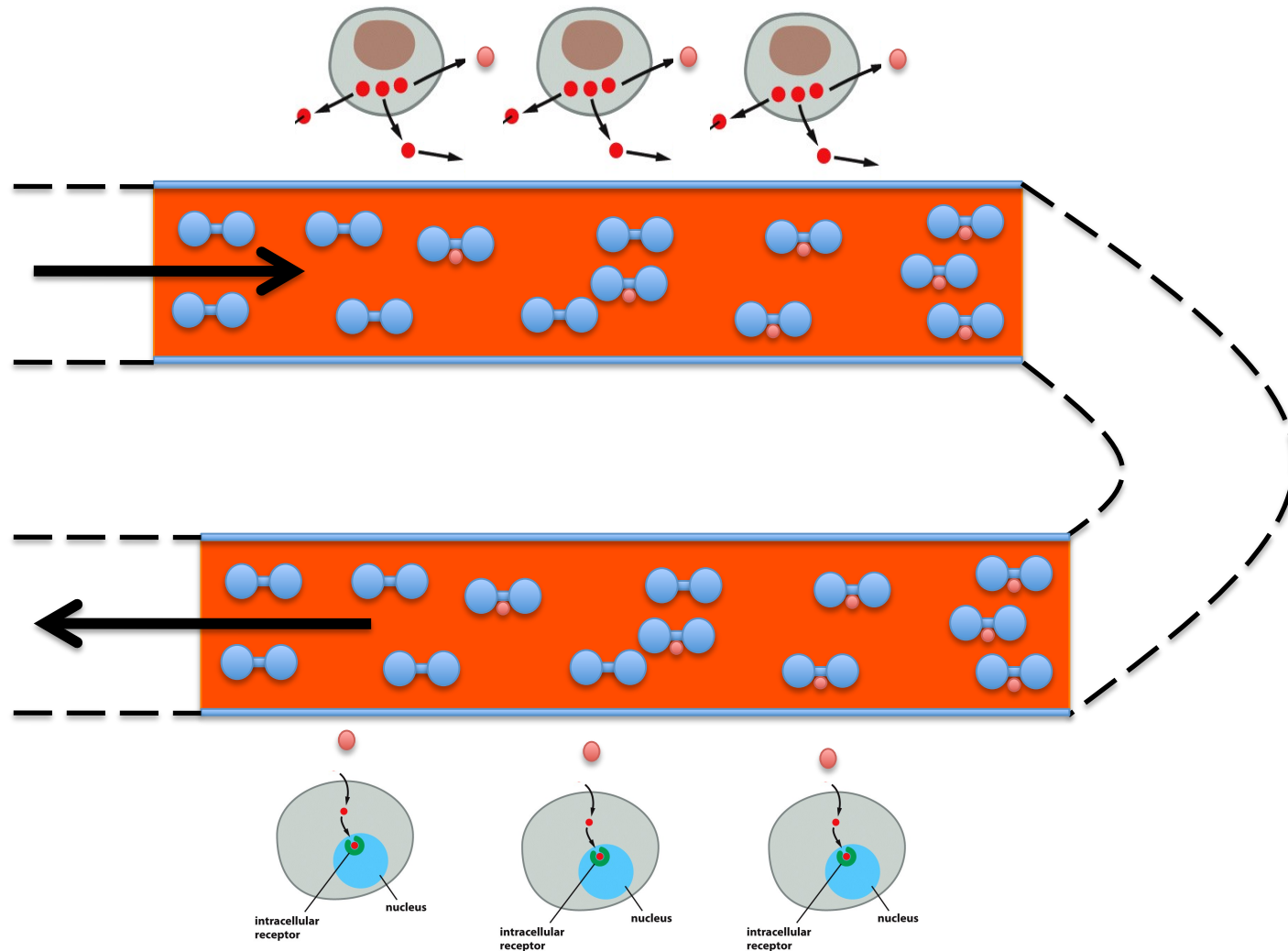


Consequences of Hydrophobic Hormones

- Solubility in water?
- Solubility in lipid membrane?
- How does this affect its transportation in blood?

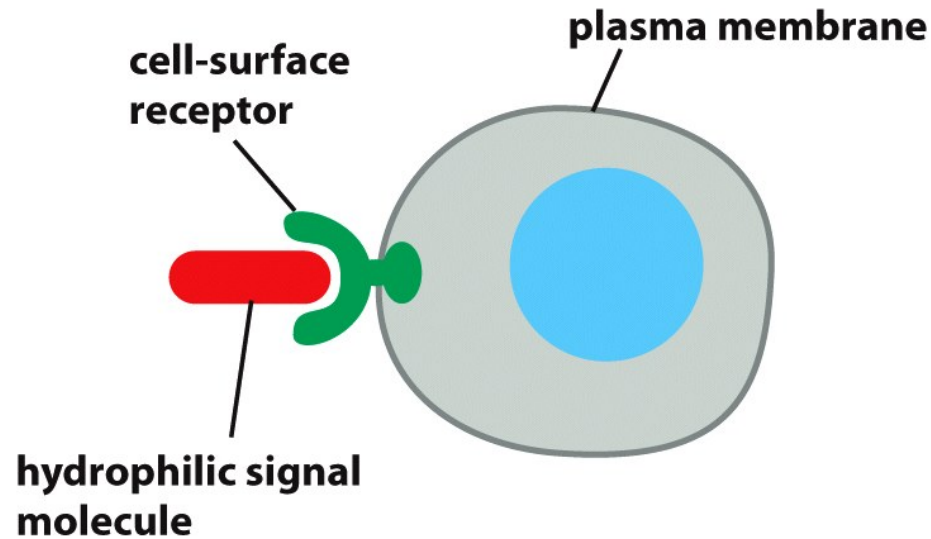


Steroid Hormones catch a ride on Carrier Proteins

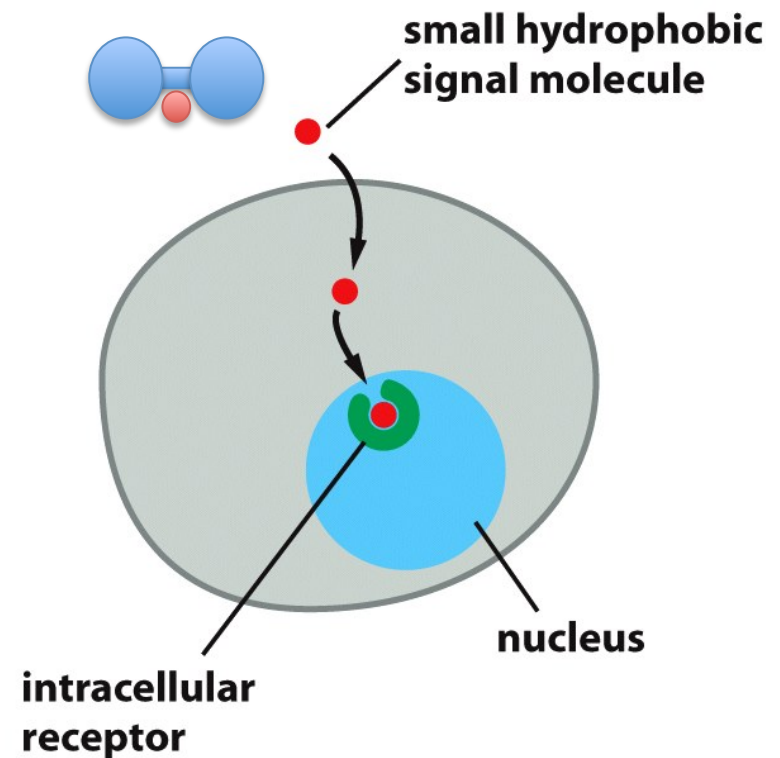


How are receptors different?

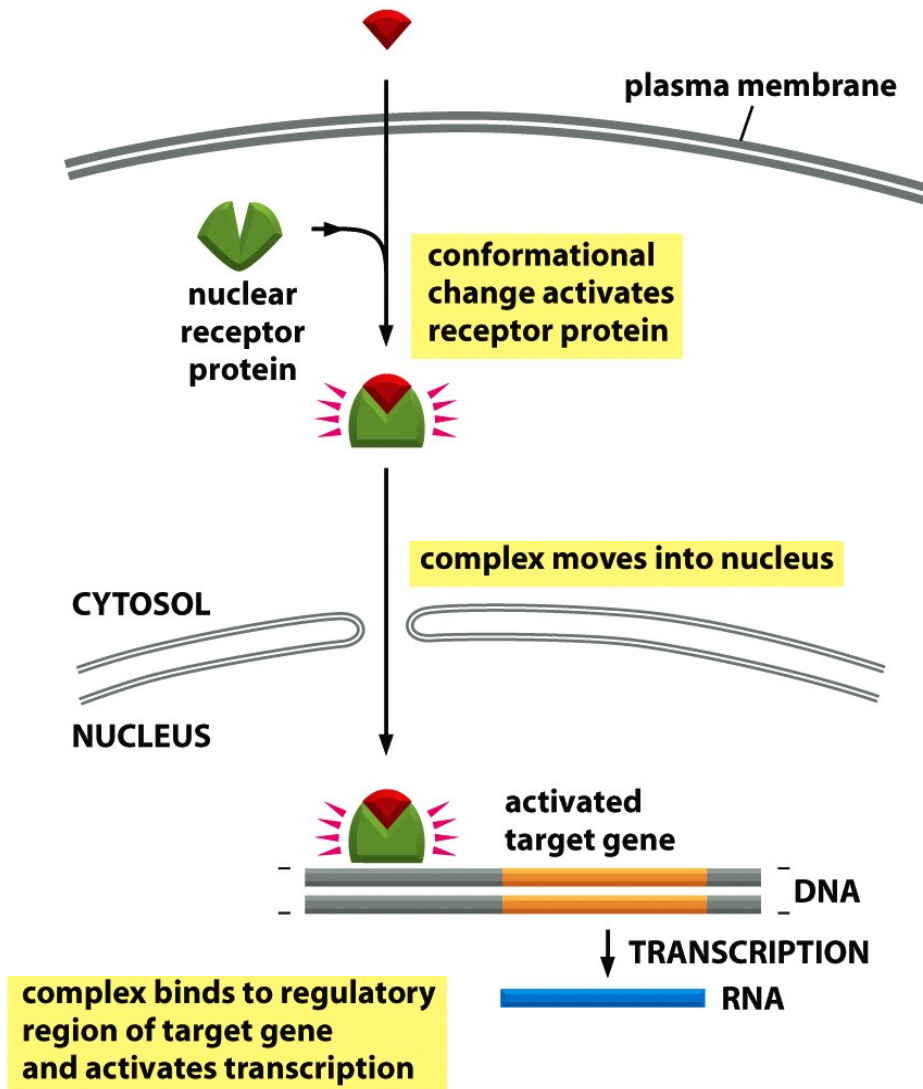
(A) CELL-SURFACE RECEPTORS



(B) INTRACELLULAR RECEPTORS



Basic Nuclear Receptor Activation





Lets get specific: The Estrogen Receptor

- A nuclear receptor protein
- Binds Estrogen and affects DNA transcription
- Changes pattern of gene expression
- Affect on organism is slow
 - minutes to days

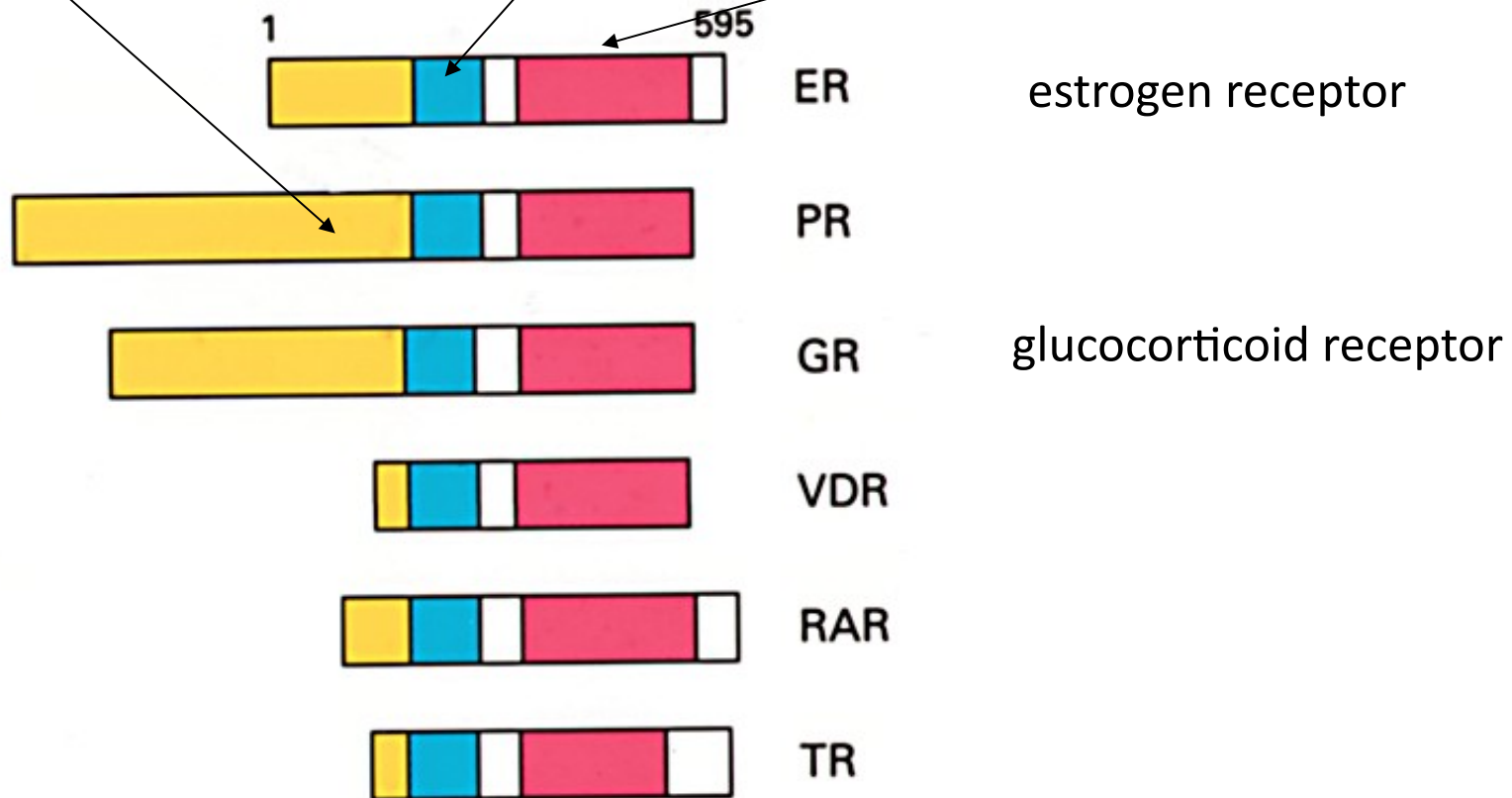


Nuclear Receptor Subfamily

Yellow shows the highly variable activation domain

Blue shows the highly conserved DNA binding domain ~66 amino acids

Red shows the hormone binding domain





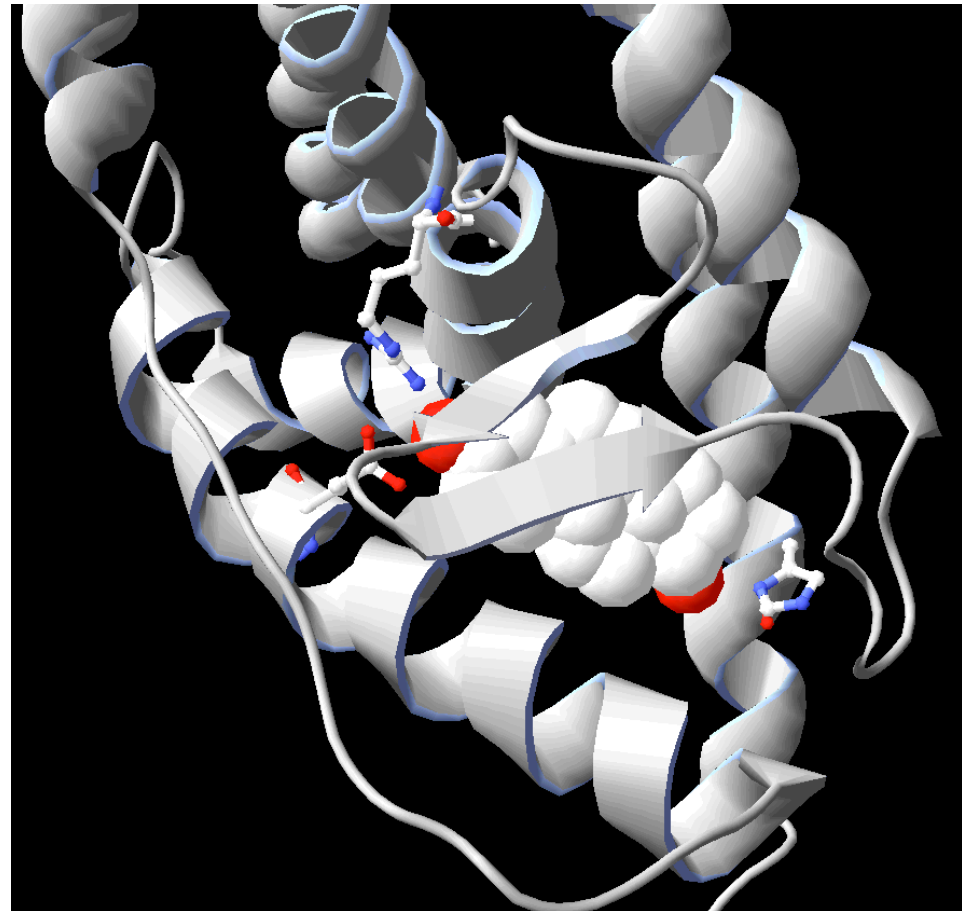
1a52 in FirstGlance

- <http://oca.weizmann.ac.il/oca-docs/fgij/fg.htm?mol=1a52>
- Hide, then hide one of the ER chains
- Contacts, then click on the estrogen
 - Will have to rotate to find it, as it is buried in center of ER ligand binding domain
- Select 4th view, uncheck all
 - Check Show putatively hydrogen bonded non-water
 - Then look at hydrophobic interactions



Estrogen bound to Ligand binding domain

- Deep pocket
- Specific H-bonds
- Very Hydrophobic
- Not covalently bound





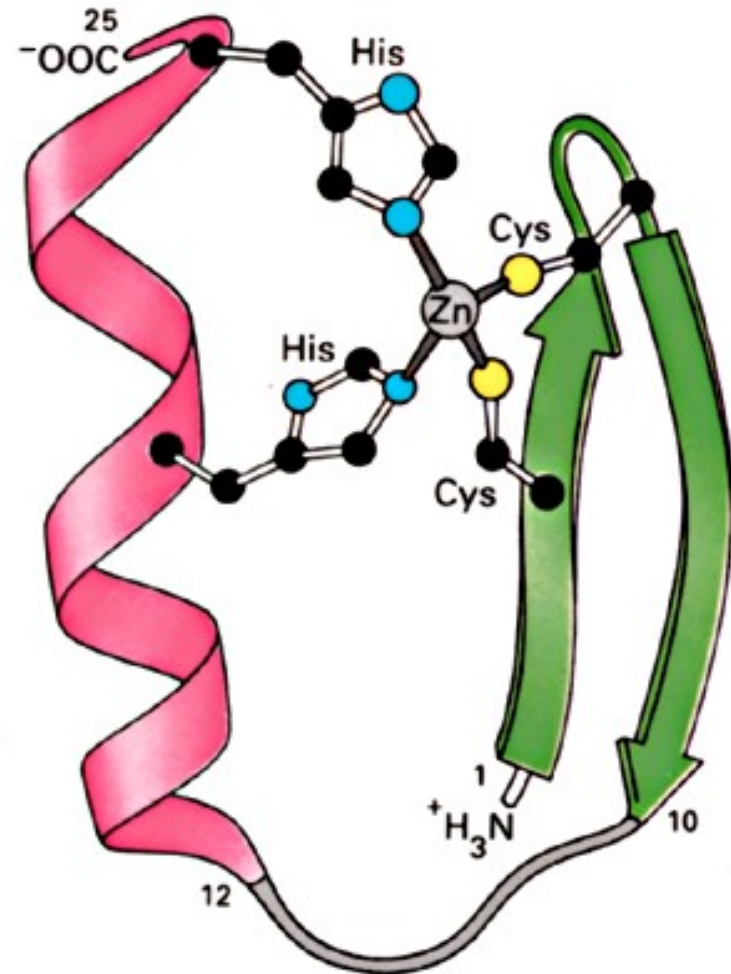
Binding Triggers Activity

- How could this happen?
- We know:
 - Only active when bound to ligand
 - One estradiol per ER monomer
 - Forms dimers
 - Ligand binding domain is connected to DNA binding domain (Not shown yet)



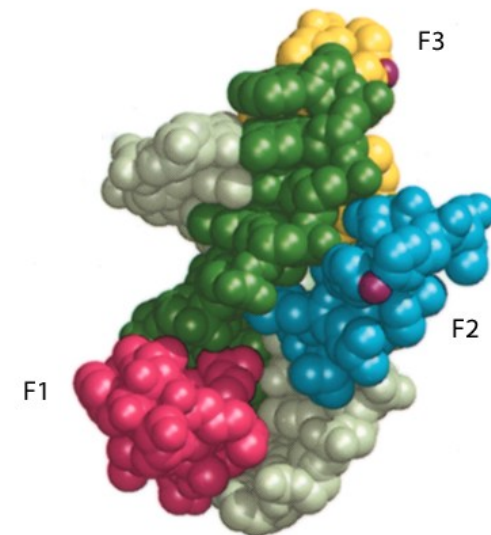
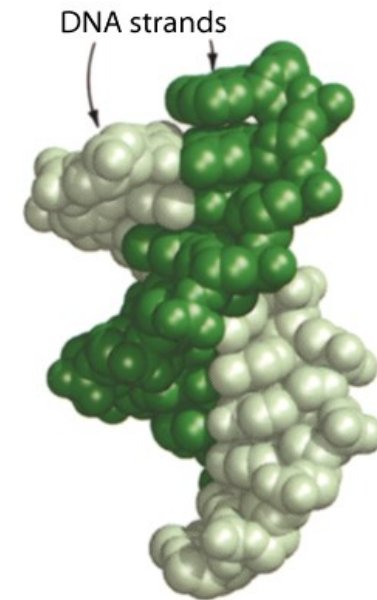
DNA Binding Domain

- Zn finger
- >700 genes include this fold
- Zif268, a classic Zn finger is shown here
- The helix interacts with the DNA



Steroid Receptors use Zn fingers

- Structural motif is highly versatile
- Proteins can have 1 to 37 of these fingers
- More fingers, longer DNA sequence recognized
- Recognition is based of non-covalent, complementarity between amino acids on helix and base pair sequence of DNA



Steroid receptors recognize related DNA sequences

5'—NAG **AA**CANNNTG**TT**CTN—3'

3'—NTC**TT**GTNNNAC**AA**GAN—5'

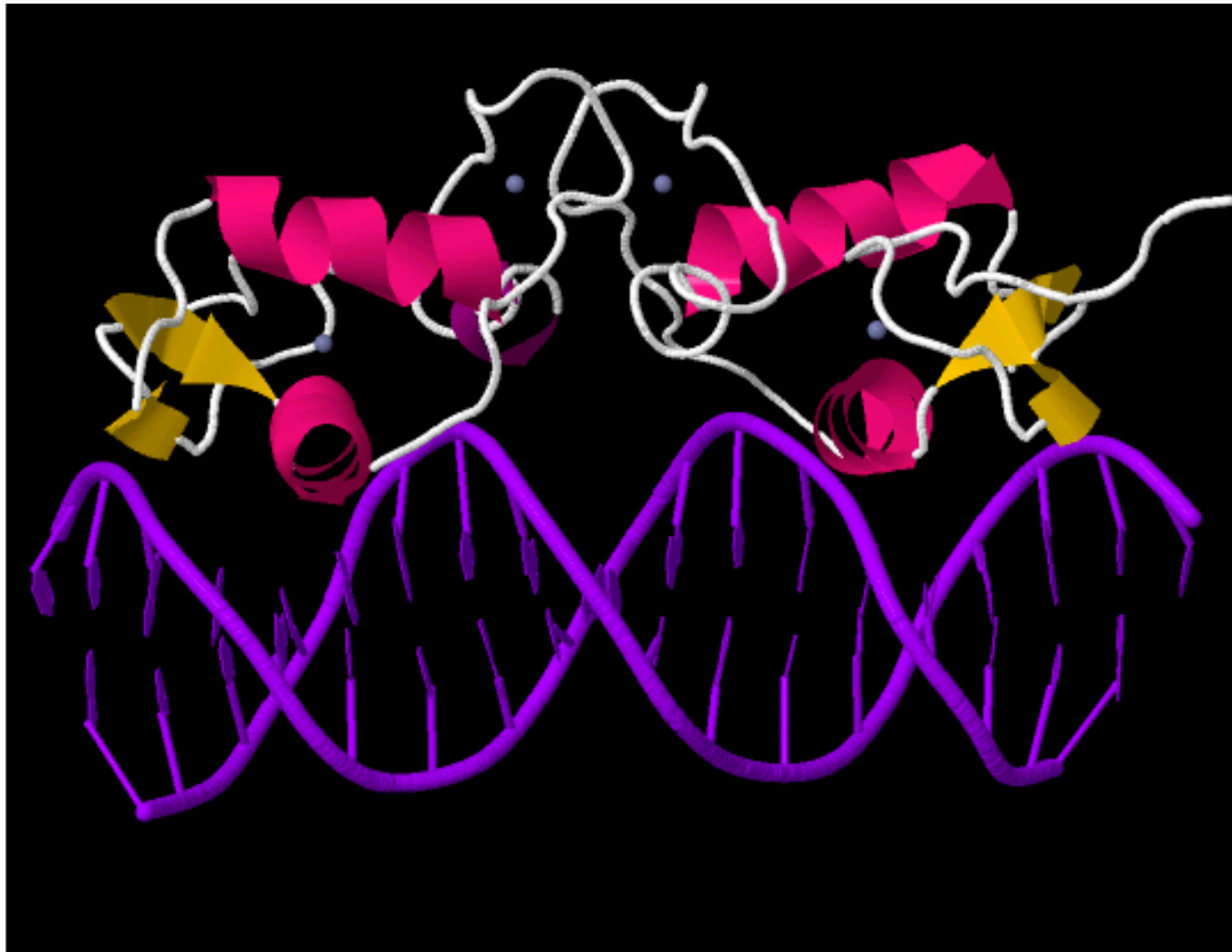
**Glucocorticoid response element
(GRE)**

5'—NAG **GT**CANNNTG**AC**CTN—3'

3'—NTC**CA**GTNNNACT**TG**GAN—5'

**Estrogen response element
(ERE)**

ER DNA binding domain



PDB 1HCQ



Un-natural Signaling?

- Non-Natural non-steroidal ligands
- Environmental Estrogens
 - Phytoestrogens from plants but remember plants don't have cholesterol so must be non-steroidal pathways to derivatives.
 - Xenoestrogens: “Other” estrogens
 - DDT (the most potent estrogenic mimic known, much stronger than estrogen)
 - bisphenol A – Nalgen recalled its plastic water bottles due to this compound

