

Biochem 03 Cell Communication

November 4, 2009

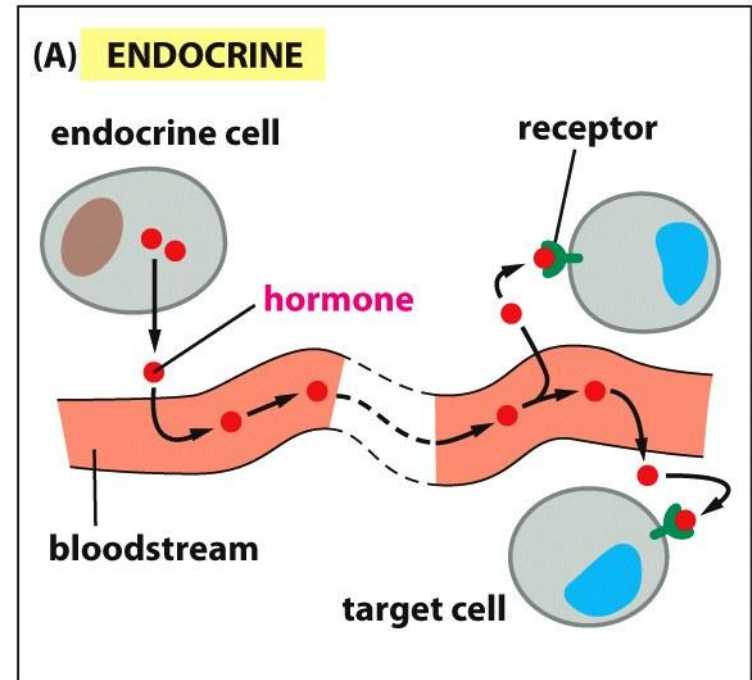
- **Function: Signal Transduction**

- **Long term acting signals**

- Steroid Hormones
- Non Steroid Hormones (peptides)

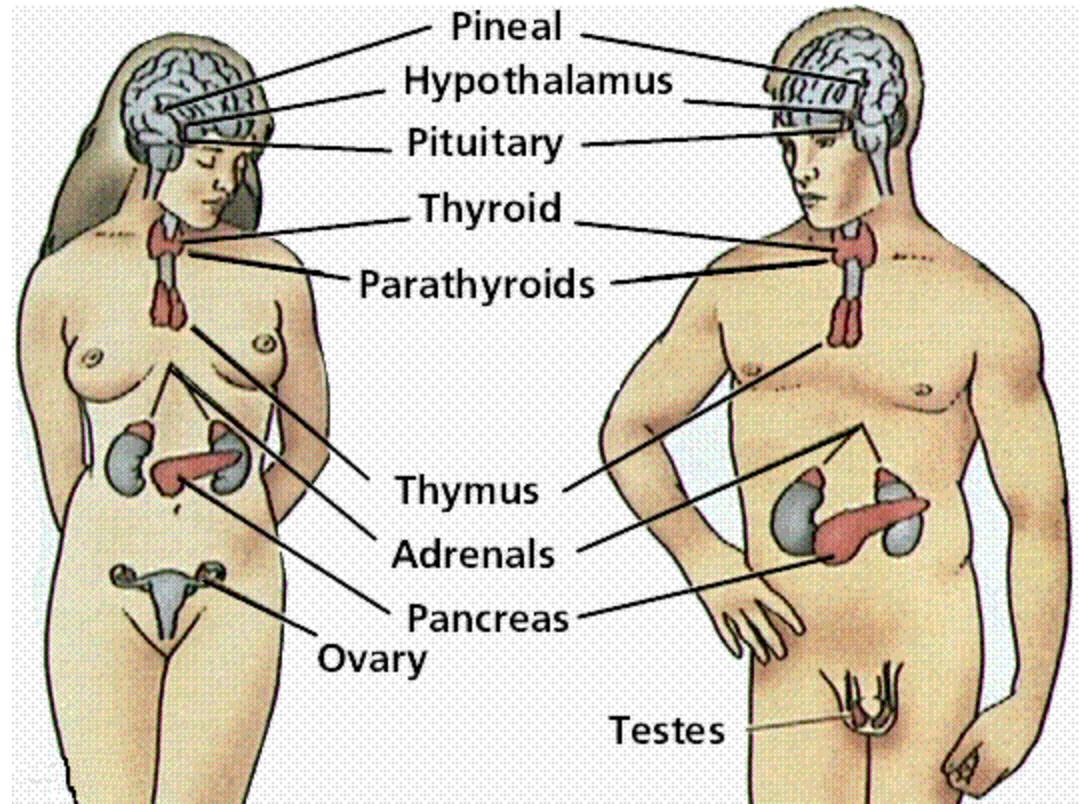
- **Short term acting signals**

- Nitric oxide, NO

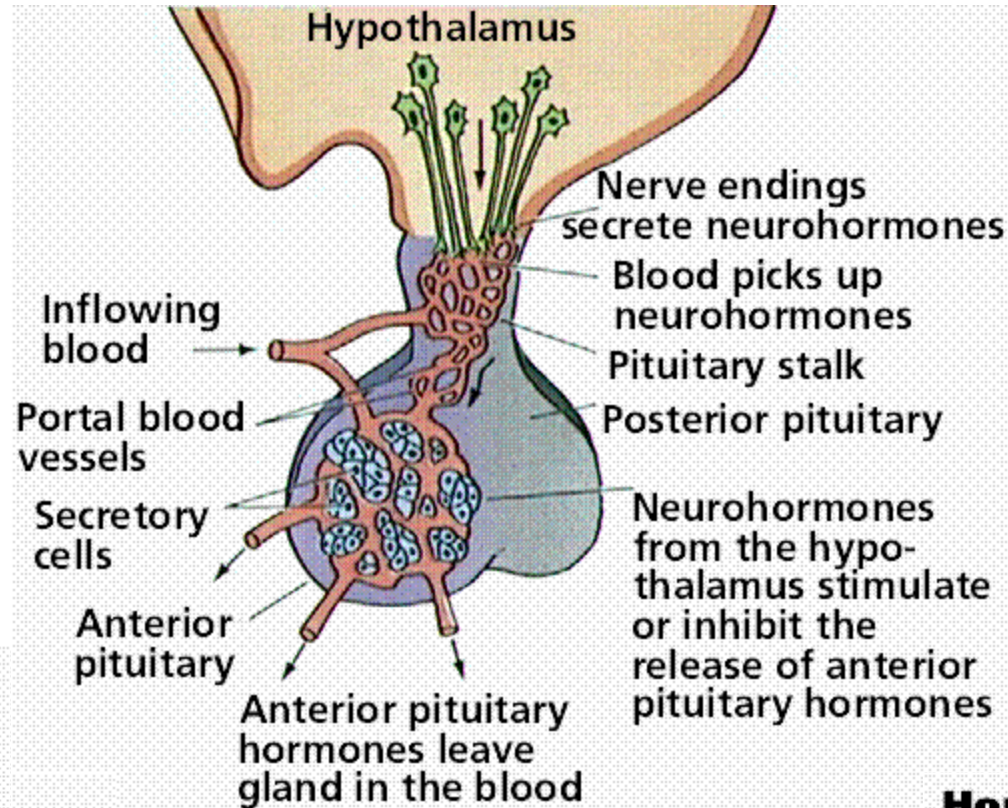


Endocrine System

- Small molecules are released from these glands into the bloodstream where they travel to a distant site and change the pace or architecture of the target tissue.
- Hypothalamus in the brain is the mission control center



Endocrine System



Anterior Pituitary

Hormones produced and released:

Thyrotropin
Adrenocorticotropin
Luteinizing hormone
Follicle-stimulating hormone

Growth hormone
Prolactin
Melanocyte-stimulating hormone
Endorphins
Enkephalins

Posterior Pituitary

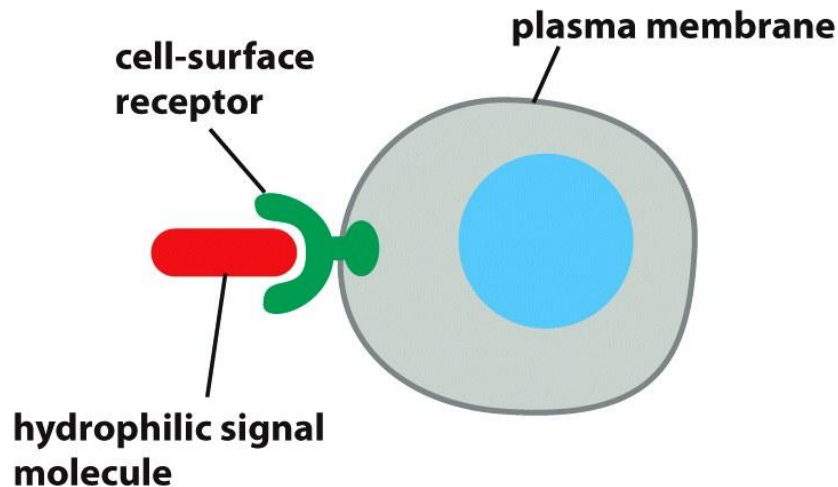
Hormones released:

Oxytocin
Vasopressin

Most of these
are PEPTIDE
HORMONES

Hormones enter cells through different methods depending on their chemical nature

(A) CELL-SURFACE RECEPTORS



(B) INTRACELLULAR RECEPTORS

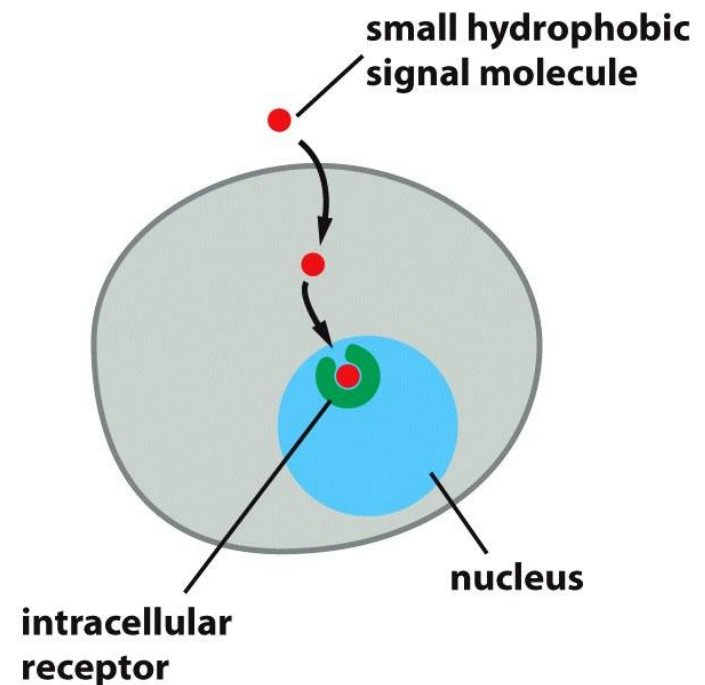


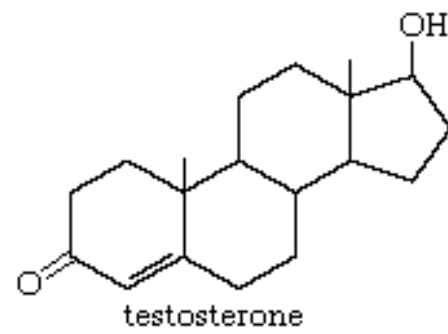
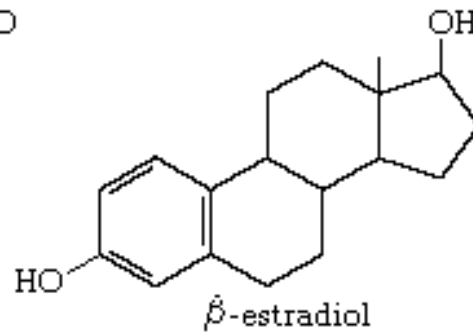
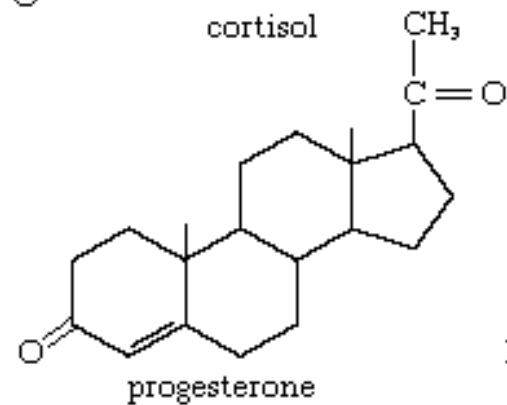
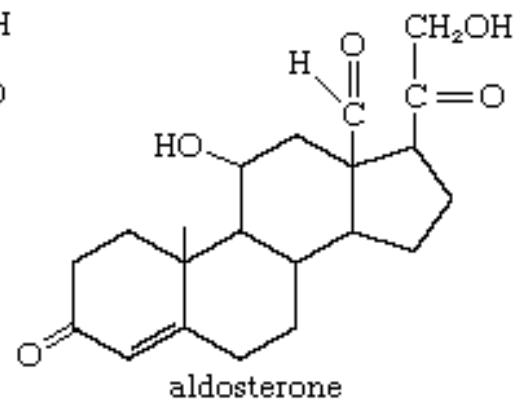
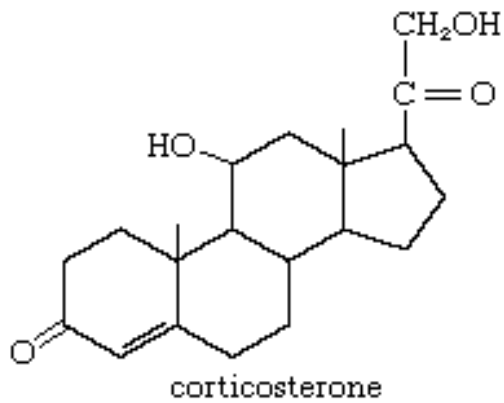
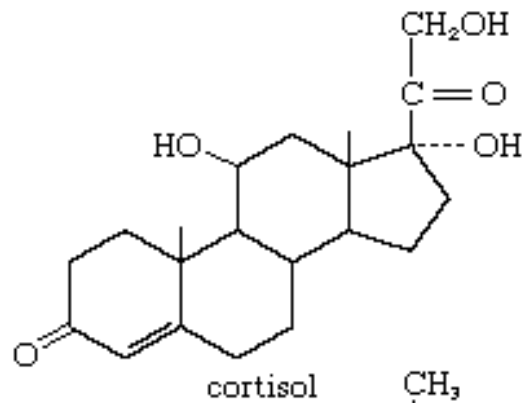
Figure 16-8 Essential Cell Biology 3/e (© Garland Science 2010)

Peptide hormones

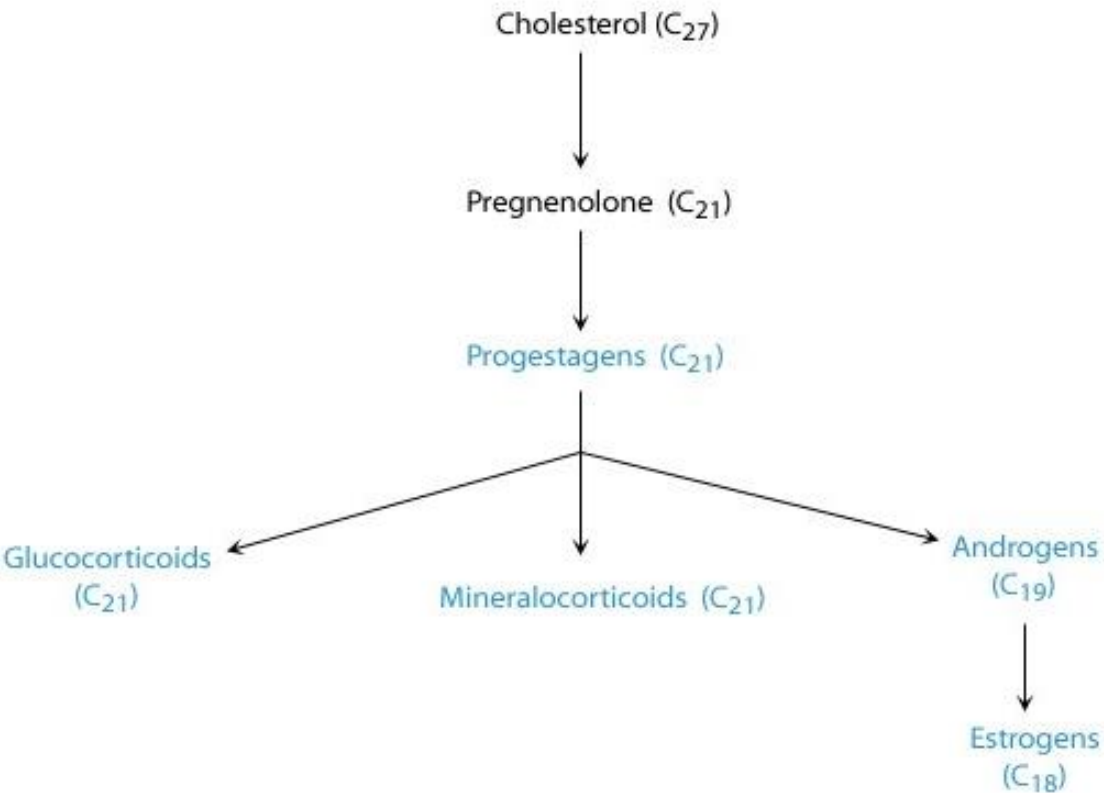
Steroid hormones

Steroid Hormones

- are small molecules
- all exhibit lots of chemical similarity
- all are fundamentally non-polar, hydrophobic



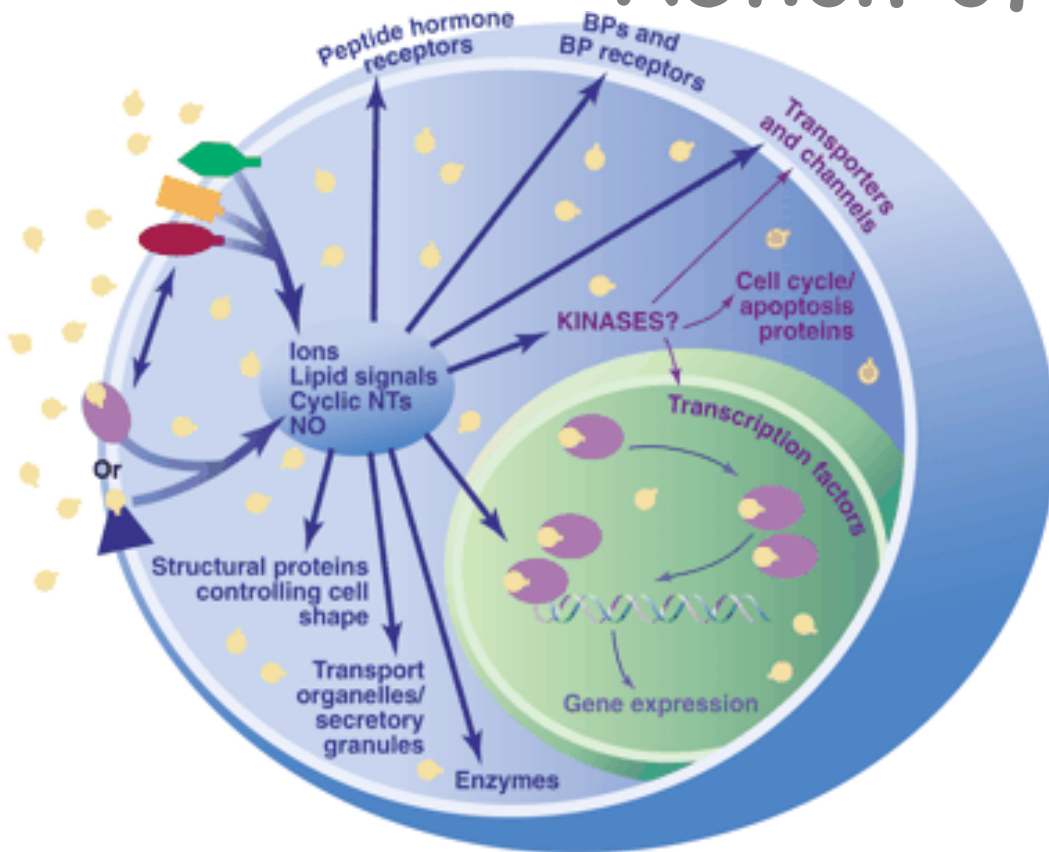
Steroid Synthesis



- derived from cholesterol
- grouped by the receptors to which they bind:

- glucocorticoids
- mineralocorticoids
- androgens
- estrogens
- progesterone
- Vitamin D a sixth closely related hormone system with homologous receptors


Action of Steroids



 Nuclear steroid receptor

 Steroid ligands

 Alternative steroid protein for the membrane

 Variety of other membrane proteins which may directly interact with steroid receptors in the plasma membrane

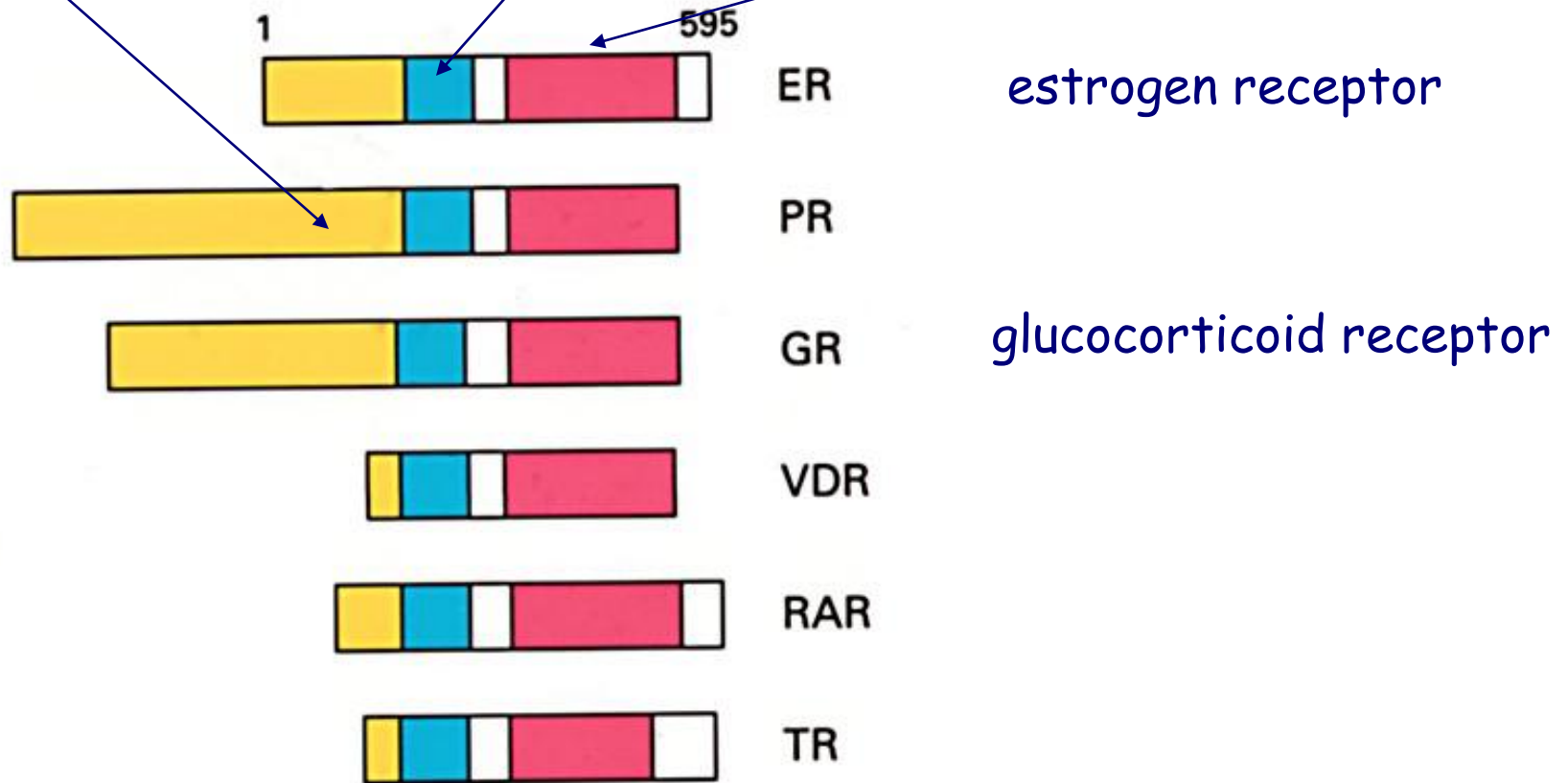
- bind to receptors
- complex migrates to the nucleus- binds to DNA
- binding to DNA affects transcription
- the **pattern** of gene expression is changed
- the time scale for this event is slow (minutes to days)

Nuclear Receptor Subfamily

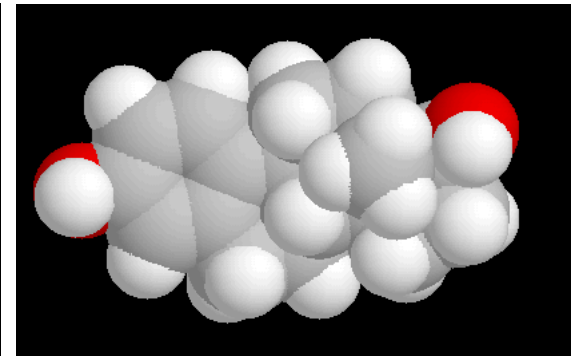
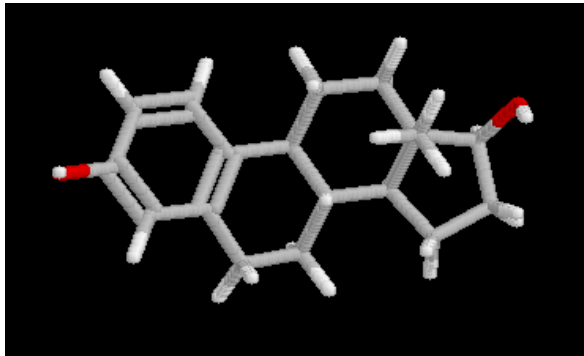
Yellow shows the highly variable activation domain

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

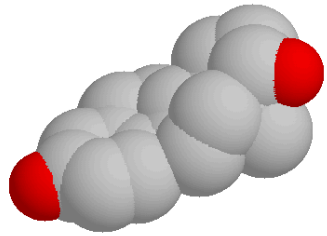
Red shows the hormone binding domain



Steroid Hormones

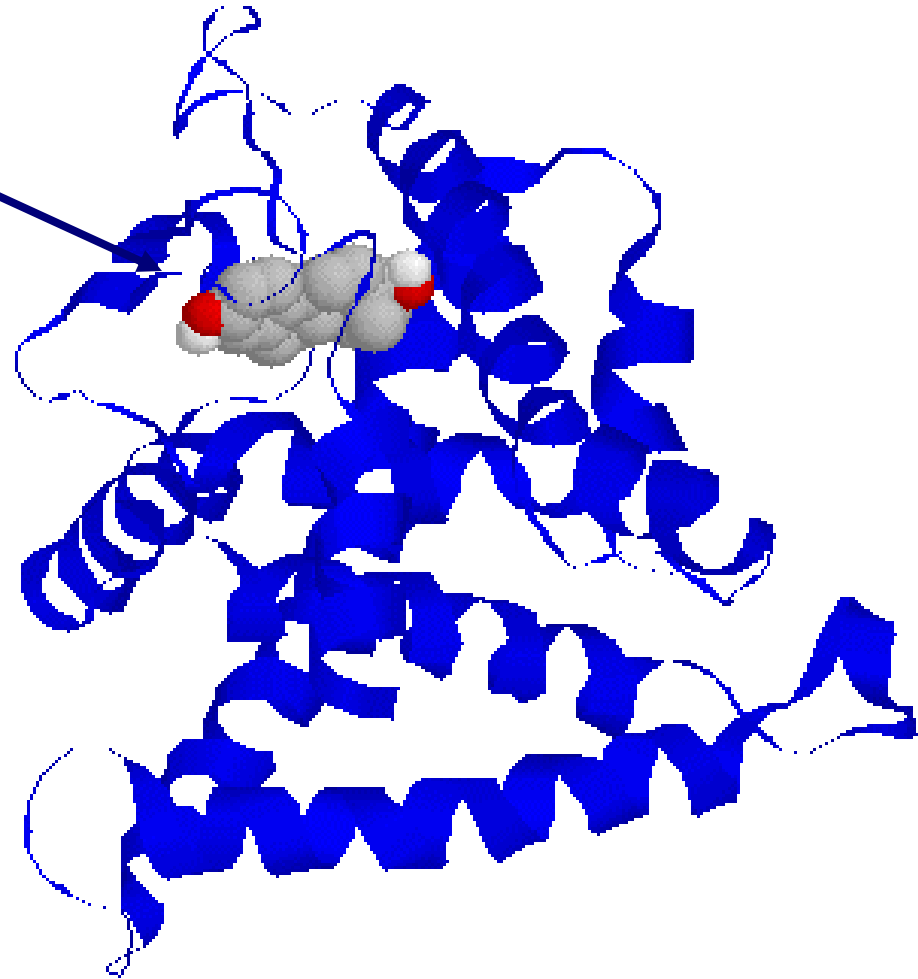


Estrogen Receptor Hormone binding domain



Estrogen

Estradiol binds in a deep cleft of a binding site in this mostly helical 240 residue domain of ER. Somehow this gets communicated to DNA binding domain



ER Hormone binding domain

Structure 1A52

<http://www.pdb.org/pdb/explore.do?structureId=1A52>

RCSB PDB : Jmol Viewer - Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://www.pdb.org/pdb/explore/jmol.do?structureId=1A52&biomnumber=1

Amherst College Camp... iGoogle Facebook | Home la vie en rose

RCSB PDB : Jmol Viewer

PROTEIN DATA BANK

An Information Portal to Biological Macromolecular Structures

As of Tuesday Nov 03, 2009 at 4 PM PST there are 61248 Structures | PDB Statistics

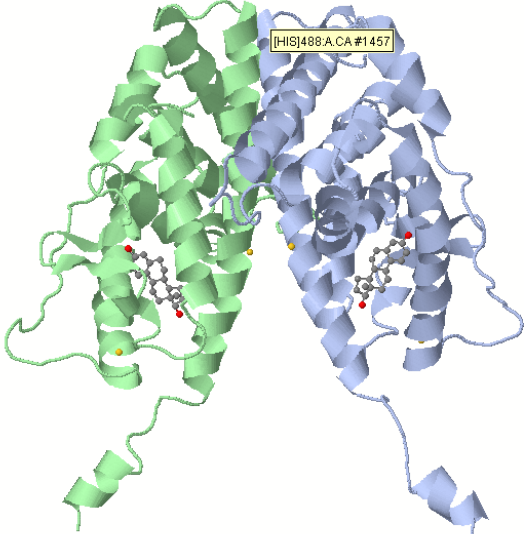
WHAT'S NEW | HELP | PRINT

PDB ID or keyword Search ? | Advanced Search

Summary Derived Data Sequence Seq. Similarity Literature Biol. & Chem. Methods Geometry Links

ESTROGEN RECEPTOR ALPHA LIGAND-BINDING DOMAIN COMPLEXED TO ESTRADIOL **1a52** Display Files ▾
Download Files ▾
Share this Page

Jmol Version 11.6



Jmol_S

Tip: right-mouse click on Jmol to get access to additional Jmol functionality.

http://www.pdb.org/pdb/explore/jmol.do?structureId=1A52&biomnumber=1

ER Hormone binding domain

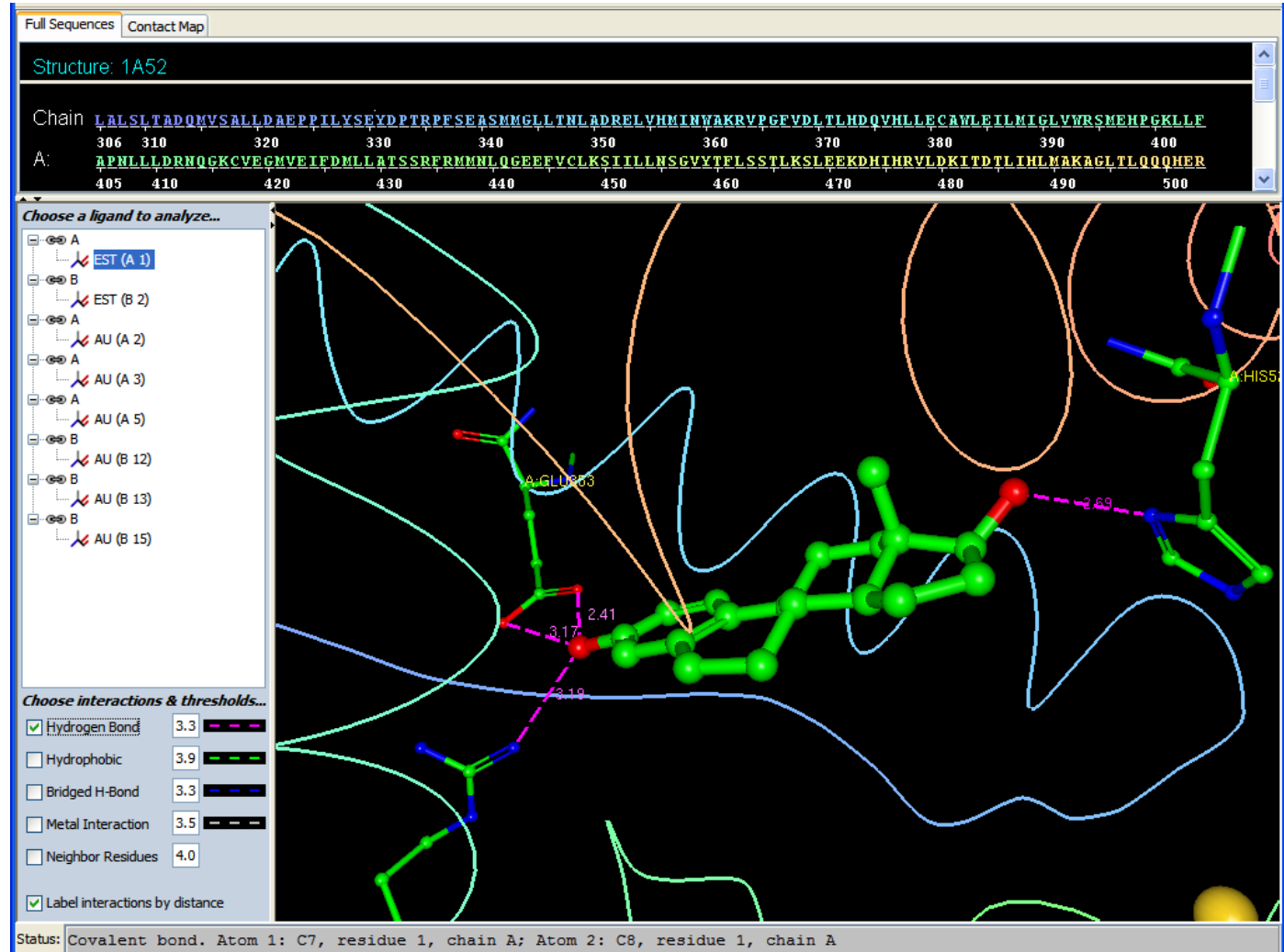
Structure 1A52

Hydrogen Bonds

Ring A: Oxygen



Ring D Oxygen



ER Hormone binding domain

Structure 1A52

Hydrophobic Int.
@3.7 Å

Ring A:

Ring B:

Now change
distance to 3.8 Å
and see what
other interactions
you see

RCSB PDB Ligand Explorer 3.5 (powered by the MBT): 1A52

File Analysis Help

Full Sequences Contact Map

Structure: 1A52

Chain: L A L S L T A D Q M V S A L L D A E P P I L Y S E Y D P T R P F E S A S M M G L L T N L A D R E L V H M I N W A K R V P G F V D L T L H D Q V H L L E C A W L E I L M I G L V W R S M E H P G K L L F
306 310 320 330 340 350 360 370 380 390 400
A: A P N L L L D R N Q G K C V E G M V E I F D M L L A T S S R F R M M N L Q G E E F V C L K S I I L L N S G V Y T F L S S T L K S L E E K D H I H R V L D K I T D T L I H L M A K A G L T L Q Q Q H E R
405 410 420 430 440 450 460 470 480 490 500

Choose a ligand to analyze...

- EST (A 1)
- EST (B 2)
- AU (A 2)
- AU (A 3)
- AU (A 5)
- AU (B 12)
- AU (B 13)
- AU (B 15)

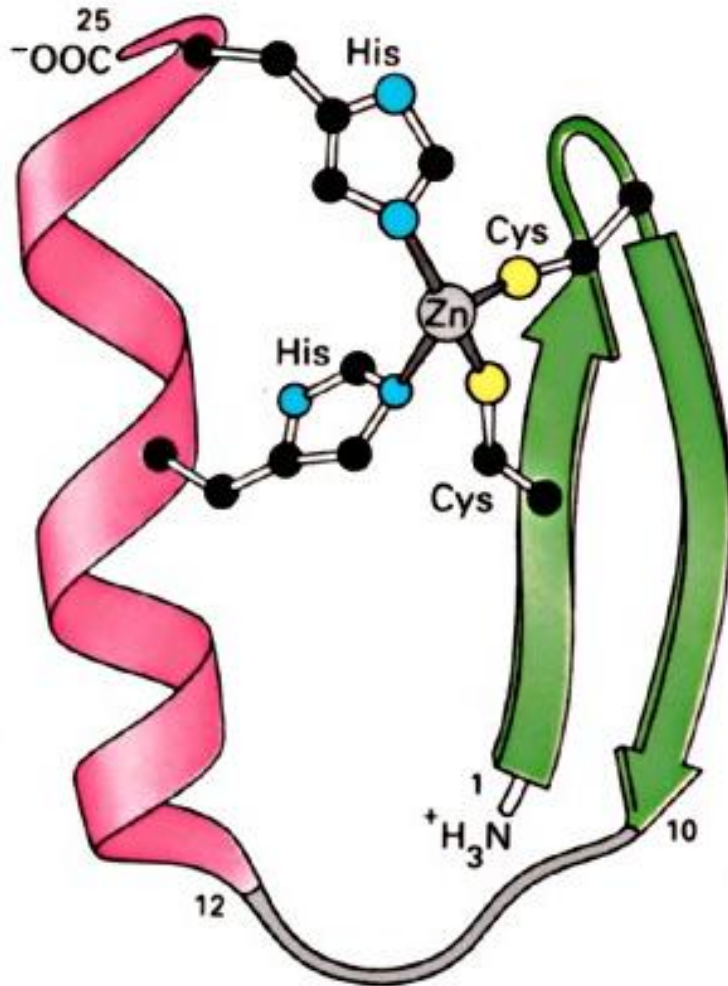
Choose interactions & thresholds...

- Hydrogen Bond 3.3
- Hydrophobic 3.7
- Bridged H-Bond 3.3
- Metal Interaction 3.5
- Neighbor Residues 4.0
- Label interactions by distance

Status: Covalent bond. Atom 1: CG, residue 391, chain A; Atom 2: CD2, residue 391, chain A

Steroid Receptors

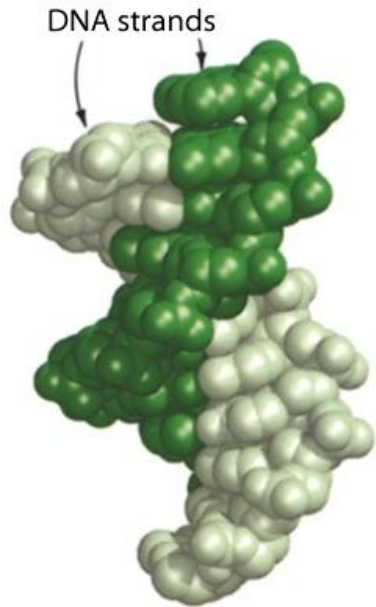
DNA binding domain



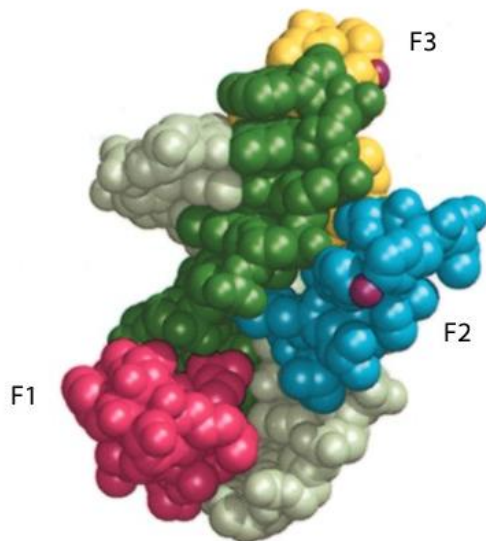
- Zn finger proteins are the 2nd largest class of proteins
- Genes for > 700 different Zn fingers in the human genome (antibodies largest)
- DNA binding domain of a classic Zinc finger Zif268 shown left
- the red helix interacts with the DNA.....How?

Steroid Receptors

DNA binding domain



- Structural motif is highly versatile (one type of structure seems to be used in 700 different ways.)
- # of Zn fingers in one protein ranges from 1 to 37
- Extended DNA sequences can be specifically recognized
- Recognition happens through complementarity between amino acid side groups on helix (blue below) and base pair sequence of DNA



Common Motifs in Steroid Receptors

What the DNA looks like...

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'

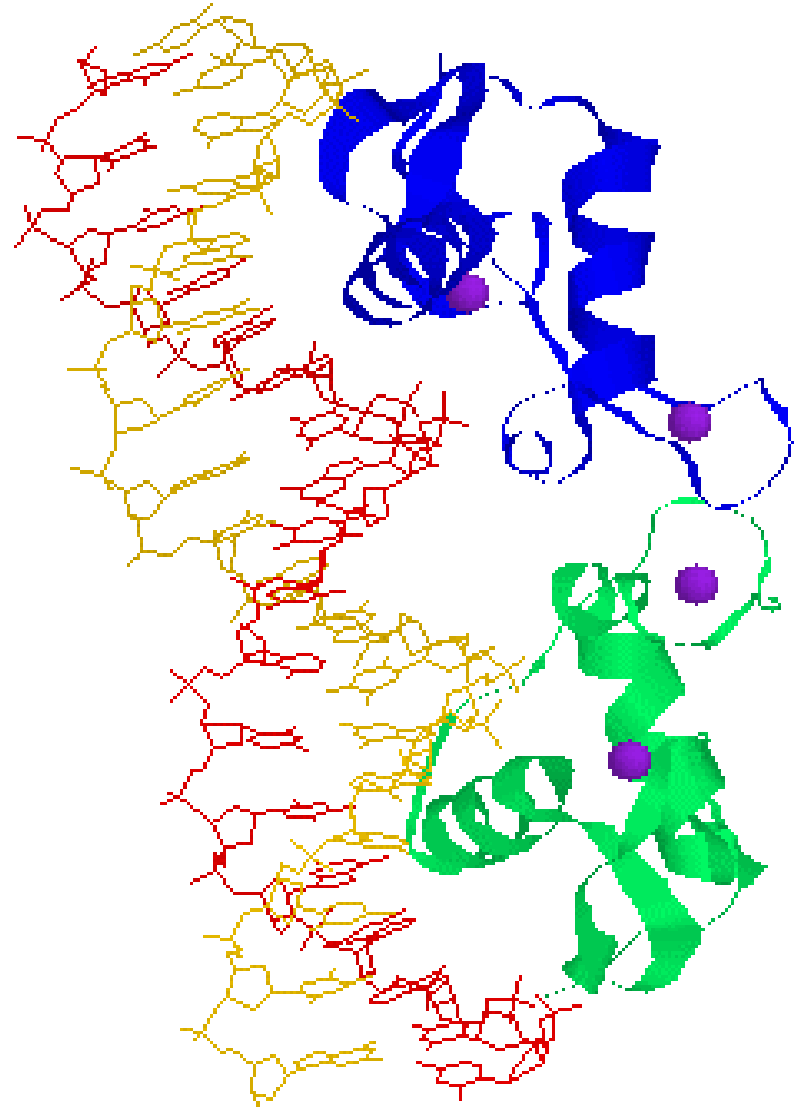
3'—NTC **CA** GTNNNAC **TG** GAN—5'

**Estrogen response element
(ERE)**

- The DNA binding domain of the receptor binds to the hormone response element on the DNA
- Changes of only two base pairs within each palindromic unit on the DNA switches the recognition from GR to ER

Estrogen Receptor * DNA binding domain

- Estrogen Receptor's DNA binding domain also a zinc cluster protein.
- Shown here is the DNA binding domain similar to glucocorticoid receptor



ER DNA binding domain

Structure 1hcq

<http://www.pdb.org/pdb/explore.do?structureId=1HCQ>

RCSB PDB : Jmol Viewer - Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://www.pdb.org/pdb/explore/jmol.do?structureId=1HCQ&ionnumber=1

Amherst College Camp... iGoogle Facebook | Home la vie en rose

RCSB PDB : Jmol Viewer

Summary | Derived Data | Sequence | Seq. Similarity | Literature | Biol. & Chem. | Methods | Geometry | Links

News & Publications
Policies
FAQ
Contact
Feedback
About Us

Deposition
All Deposit Services
Electron Microscopy
NMR
Validation Server
BioSync Beamline
Related Tools

Search
Advanced Search
Latest Release
Latest Publications
Sequence Search
Ligand Search
Unreleased Entries
Browse Database
Histograms

Explorer:
Last Structure: 1HCQ

Tools
File Downloads
File Formats
Services: RESTful | SOAP
Widgets
Compare Structures

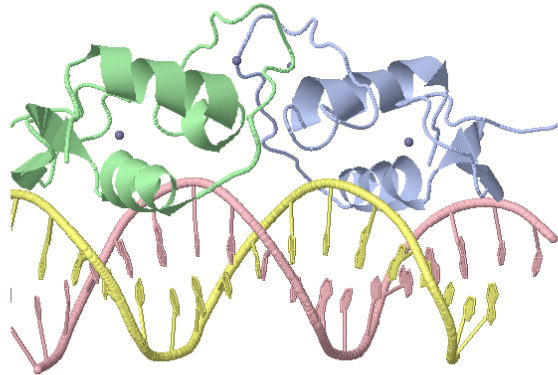
Education
Looking at Structures
Molecule of the Month
Educational Resources

THE CRYSTAL STRUCTURE OF THE ESTROGEN RECEPTOR DNA-BINDING DOMAIN BOUND TO DNA: HOW RECEPTORS DISCRIMINATE BETWEEN THEIR RESPONSE ELEMENTS

1hcq

Display Files
Download Files
Share this Page

Jmol Version 11.6



Tip: right-mouse click on Jmol to get access to additional Jmol functionality.

Jmol_Script

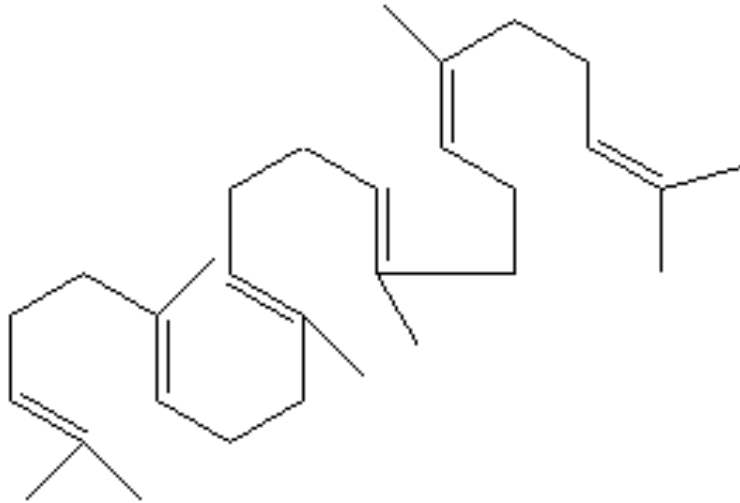
History Console Help

[ZN]598:B:ZN #1870 31.843 15.875999 127.019005

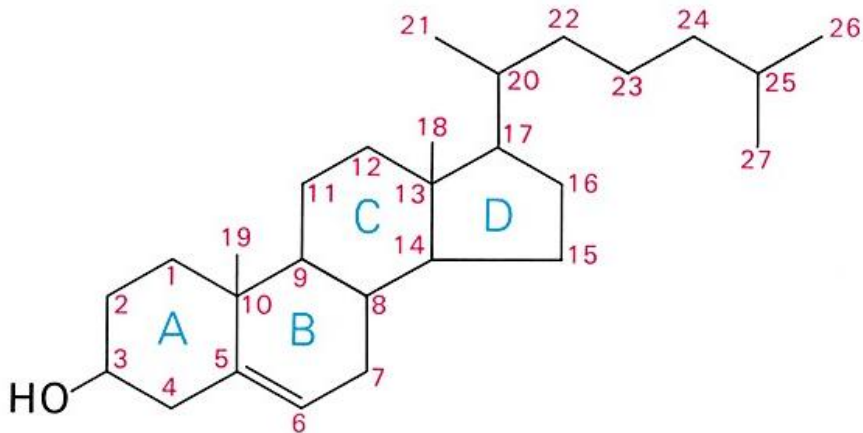
Do other types of molecules bind to this nuclear receptor subfamily?

- 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 - DDT is the most potent estrogenic mimic known, must stronger than estrogen itself in inducing proliferative cell growth, bisphenol A, THC,
 - see handout of xenoestrogens
 - see estrogen mimics under external links, signal transduction folder.

Steroid Synthesis



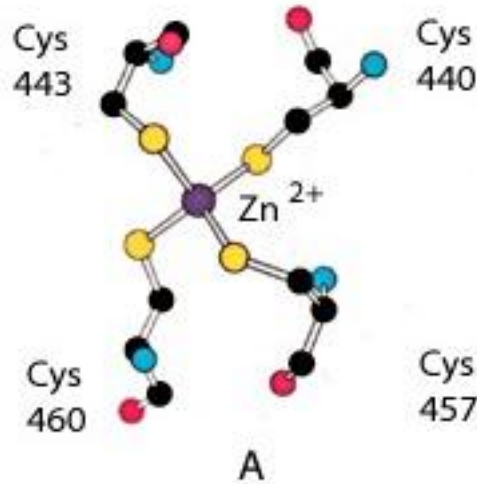
- Steroid biosynthesis starts with the fatty acid squalene, whose carbon backbone is shown here
- Synthesis occurs in the gonads and in the adrenal glands



Glucocorticoid Receptor



DNA Binding Domain of Glucocorticoid Receptor.PDB



dimeric protein (blue and yellow balls above right)

Each stabilized by a pair of zinc clusters (small purple balls)

Recognition helix fits snugly into major groove of DNA,
which widens 2 Å in the process.

Iglu.pdb from Sigler et al, Nature 1991