AT A GLANCE...

Classification of hormones

Chemical Composition

1. **Steroids** (cholesterol-derived)
Eg. Gonadal & adrenal hormones

2. **Proteins**
A. Amino-acids-derived
(i) Tyr-derived (thyroxin, catecholamines)
(ii) Trp-derived (melatonin)

B. Peptides (Insulin, Glucagon, -RH, PTH, GH, ACTH, oxytocin, ADH or vasopressin)
C. Glycoproteins (TSH, FSH, LH)

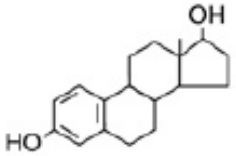
Mechanism of action

1. **Group I** (nuclear receptors)
Examples: Steroids, thyroxin, retinoids, calcitrol
2. **Group II** (transmembrane receptors)
Examples: Protein hormones (except thyroxin)

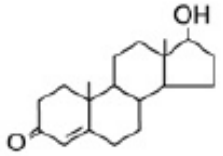
Site of synthesis

(1) Hypothalamus
(Releasing hormones)
(2) Anterior Pituitary
(Trophic hormones)
(3) Pineal
(Melatonin)
(4) Thyroid
(Thyroxin)
(5) Parathyroid
(Calcitonin)
(6) Pancreas
(Insulin, glucagon)
(7) Gonads
(Testosterone, Progesterone, Estrogens)
(8) Adrenal Cortex (glucocorticoids, mineralocorticoids-aldosterone)
(9) Adrenal medulla (catecholamines - epinephrine, nor-epinephrine)

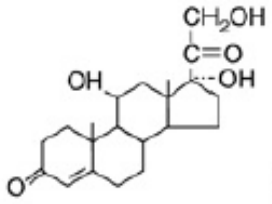
A. Cholesterol derivatives



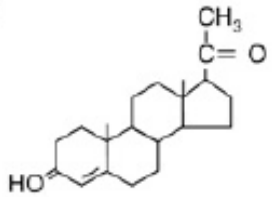
17β-Estradiol



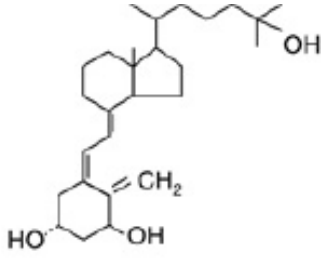
Testosterone



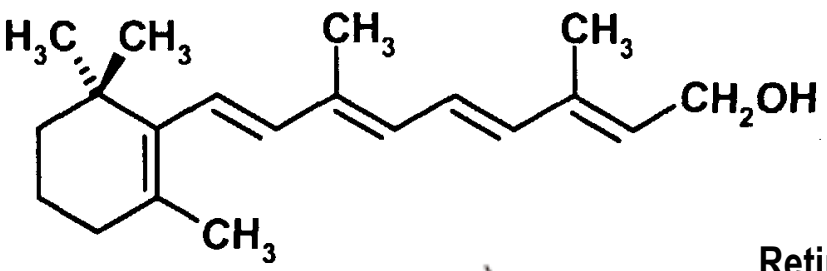
Cortisol



Progesterone

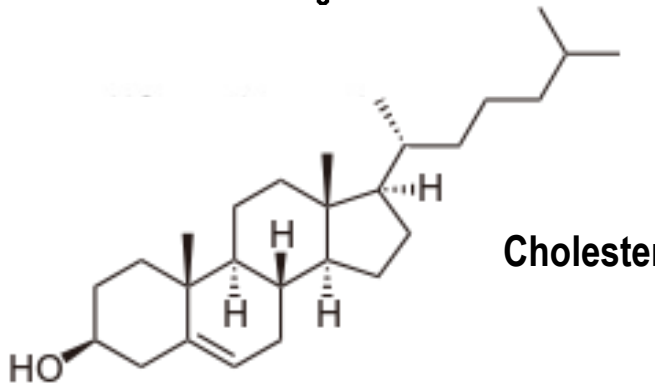


1,25(OH)$_2$-D$_3$



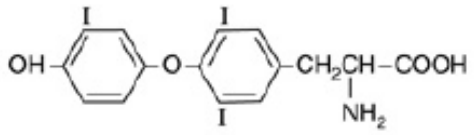
Retinoid

C18-Estrane group **C19-Androstane group** **C21-Pregnane group**

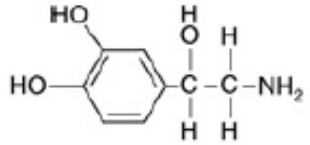


Cholesterol

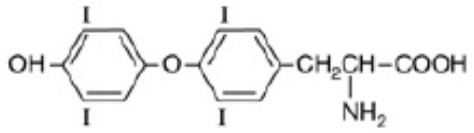
B. Tyrosine derivatives



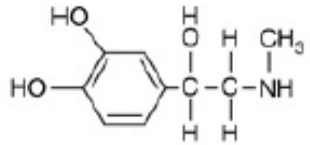
T$_3$



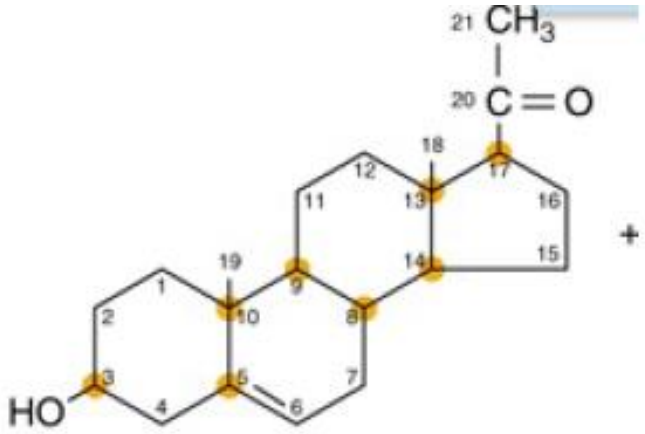
Norepinephrine



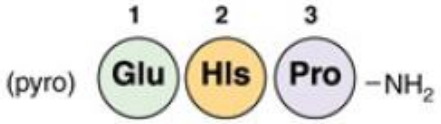
T$_4$



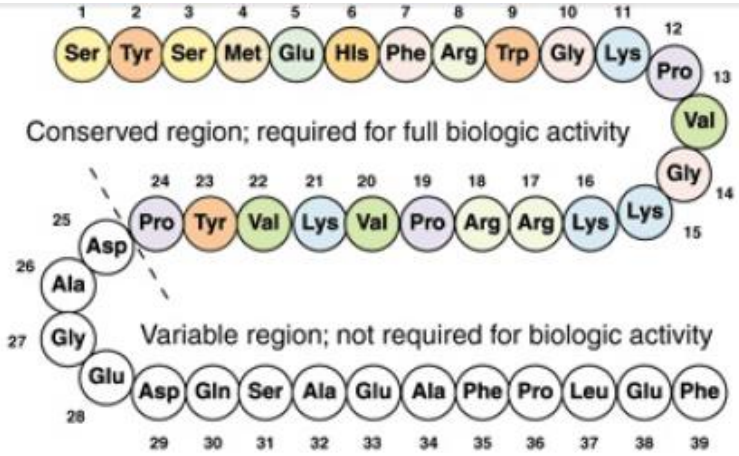
Epinephrine



C. Peptides of various sizes



TRH



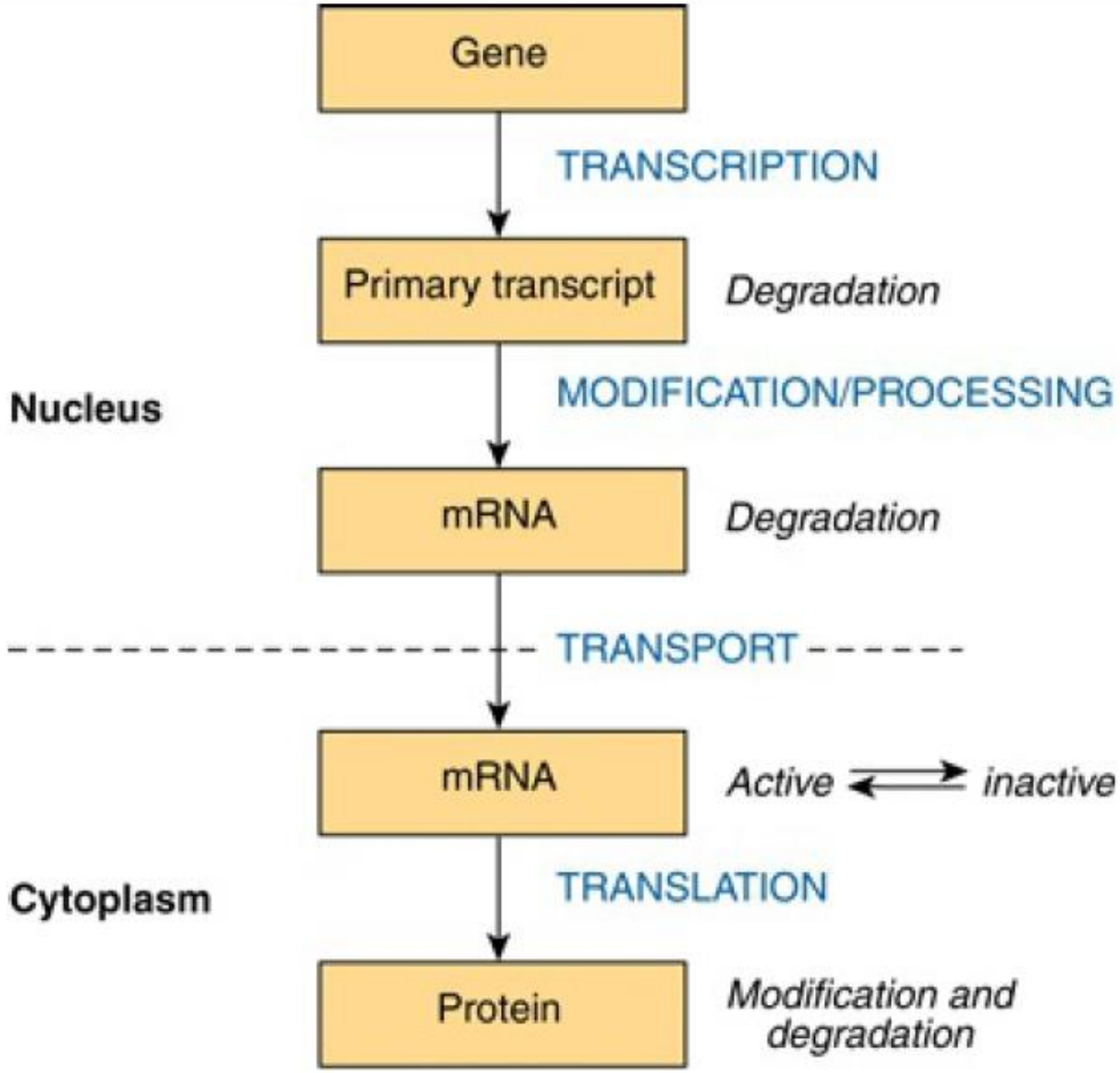
ACTH

D. Glycoproteins (TSH, FSH, LH)

common α subunits

unique β subunits

GENERAL MECHANISM OF HORMONE FUNCTIONS



General Mechanism of Actions

Group I Hormones: (steroid, thyroid, retinoid, calcitrol)

- associate with plasma transport or carrier proteins (bound-hormone)
- Free hormone – biologically active hormone → passes through lipid membrane of the target cell → binds to **receptor-proteins in the nucleus** → interacts with DNA to alter gene expression → enzyme complement change → change in cellular metabolism.
- (1) Hormone-binding domain; (2) DNA –binding domain; (3) co-regulator protein-binding domain that result in the activation (or repression) of gene transcription; and a (4) protein-binding domain to influence the intracellular trafficking of the receptor.

Group II Hormones: (Hypothalamic, Pituitary, Pancreatic)

- Associate with **cell surface/transmembrane receptors** (extracellular domain – recognition domain) - Conformational change in the receptor
- The internal functional domain generates a signal that couples hormone recognition to intracellular functions (receptor-effector coupling/signal transduction) [signal transducers]
- Activation of catalyst – producing array of chemicals– signal cascade (signal amplifiers)
- **Four types** :

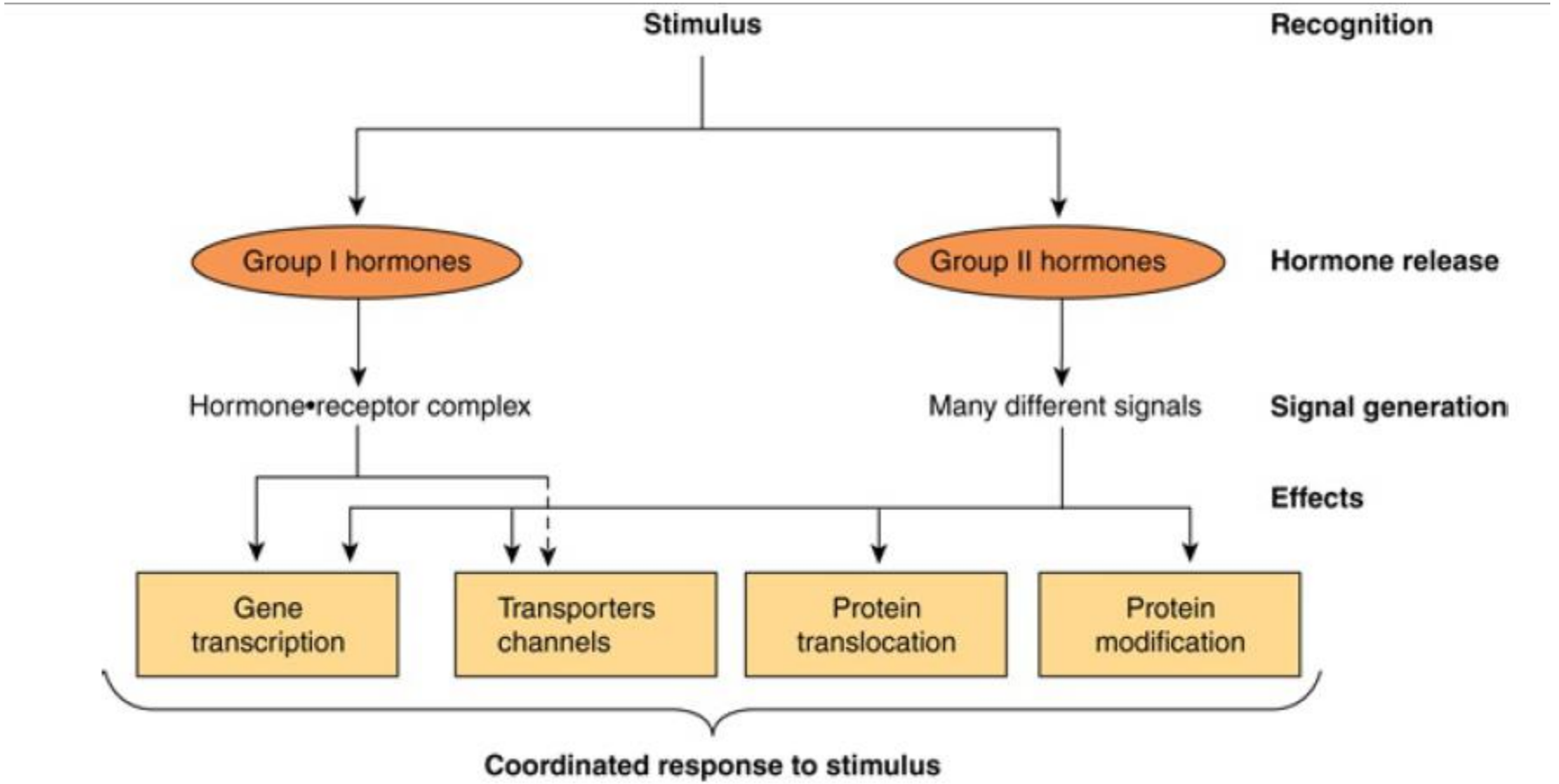
(1) Secondary messengers (cAMP, cGMP, IP3)
(2) Enzyme hydrolysis (Tyrosine kinase)
(3) Membrane potential (opening/closing of hormone-gated ion channel)
(4) Adhesion receptor from ECM to cytoskeleton

This dual purpose distinguishes the target cell receptor from the plasma carrier proteins that bind hormone but do not generate a signal.

Feature	Receptors	Transport Proteins
Concentration	Very low (thousands/cell)	Very high (billions/ L)
Binding affinity	High (pmol/L to nmol/L range)	Low (mol/L range)
Binding specificity	Very high	Low
Saturability	Yes	No
Reversibility	Yes	Yes
Signal transduction	Yes	No

Why transport proteins are important????????

- circumvent the solubility problem and thereby deliver the hormone to the target cell.
- circulating reservoir of the hormone that can be substantial, as in the case of the thyroid hormones.
- **prolonged plasma half-life** (*t1/2) – due to lack of metabolism.*
- *Binding affinity of hormone to its transporter determines the bound versus free ratio of the hormone (*the concentration of free hormone in plasma = 10–15 to 10–9 mol/L)



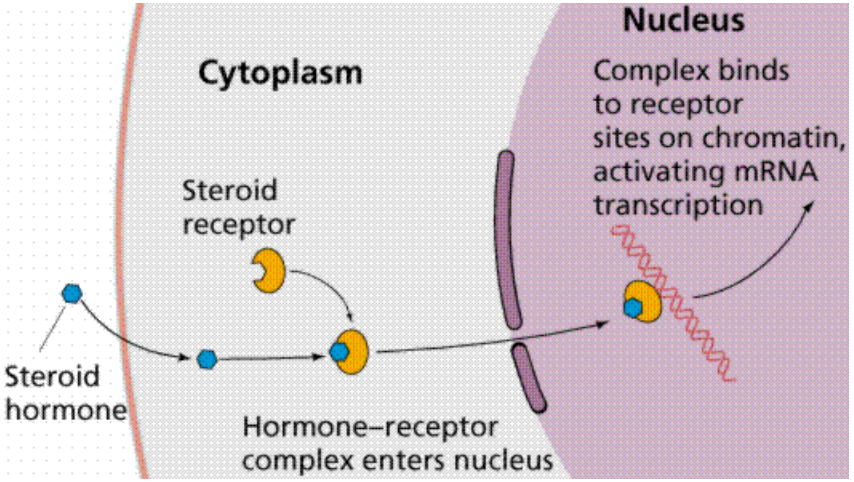
Stimulus (plural **stimuli**) is a detectable change in the internal or external environment.
The ability of an organism or organ to respond to external stimuli is called **sensitivity.**
The physiological changes occurring in the organism due to stimulus is called **response.**

Organism level: sensual perceptions (five senses & equilibrium – external stimulus; BP & homeostasis – internal stimulus)
Cellular level: pH, O_2 tension, temperature, nutrient supply, noxious metabolites and osmolarity.

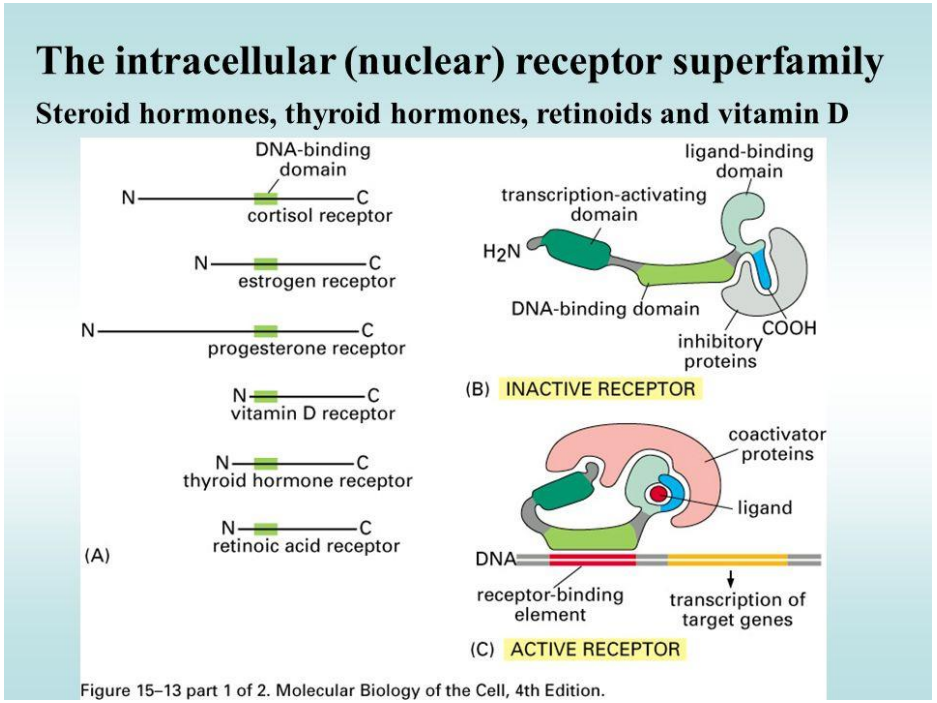
HORMONES TRANSDUCE SIGNALS TO AFFECT HOMEOSTATIC MECHANISMS -
Homeostasis or homoeostasis is the property of a system in which a variable (for example, the concentration of a substance in solution, or its temperature) is actively regulated to remain very nearly constant.

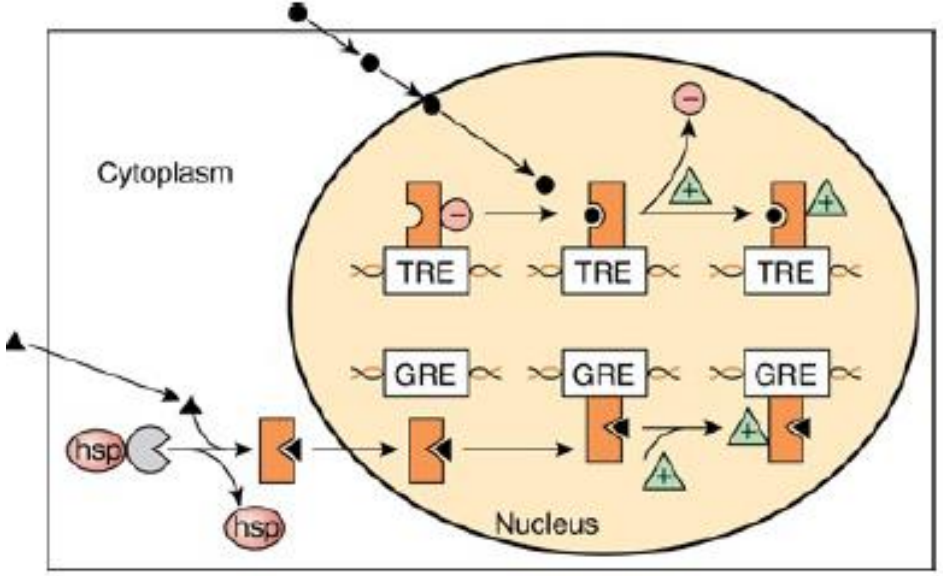
SIGNAL GENERATION

"Ligand–Receptor Complex" = Signal for Group I Hormones



Steroid Hormone-Receptor Activation & Functioning

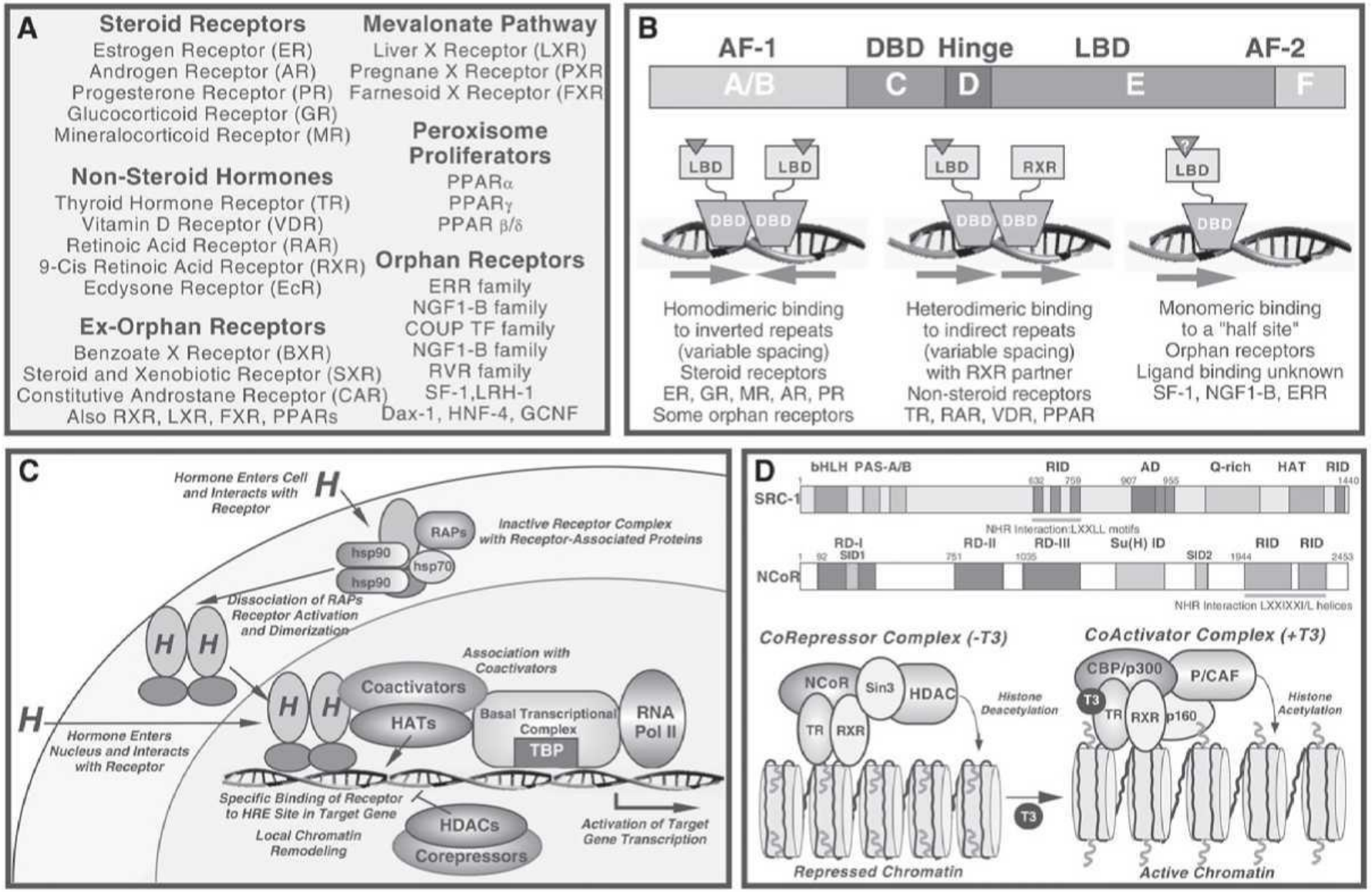




TRE = Thyroid responsive element; GRE = Glucocorticoid responsive element; hsp = heat shock protein; Glucocorticoid hormones (solid triangles); thyroid hormones and retinoic acid (•).
HRE = hormone response element = DNA sequence

- Glucocorticoid hormones (solid triangles) encounter their cognate receptor (GR) in the cytoplasm, where GR exists in a complex with heat shock protein 90 (hsp).
- Ligand binding causes **dissociation of hsp** and a **conformational change of the receptor**. NLS gets exposed.
- The receptor–ligand complex traverses the nuclear membrane and binds to DNA with specificity and high affinity at a glucocorticoid response element (GRE). This event affects the architecture of a number of TFs (green triangles), and enhance transcription.

- Thyroid hormones and retinoic acid (•) directly enter the nucleus, where their cognate heterodimeric (TR-RXR) receptors are already bound to the appropriate response elements with an associated transcription repressor complex.
- Hormone–receptor binding occurs, which again induces conformational changes in receptor leading to a reorganization of receptor (TR)-coregulator interactions (i.e. molecules such as N-CoR or SMRT).
- Ligand binding results in **dissociation of the repressor complex** from the receptor, allowing an **activator complex, consisting of the TR-TRE and coactivator, to assemble**. The gene is then actively transcribed.



Steroid hormones (glucocorticoids)

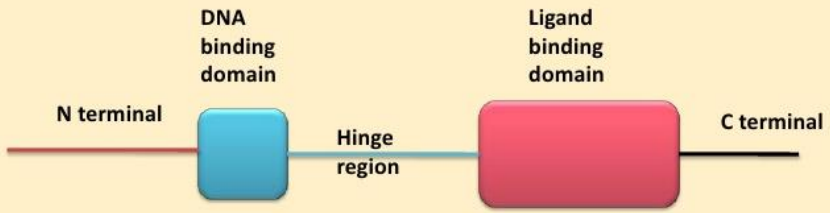
Thyroxin & Retinoids

STEROID HORMONE RECEPTOR

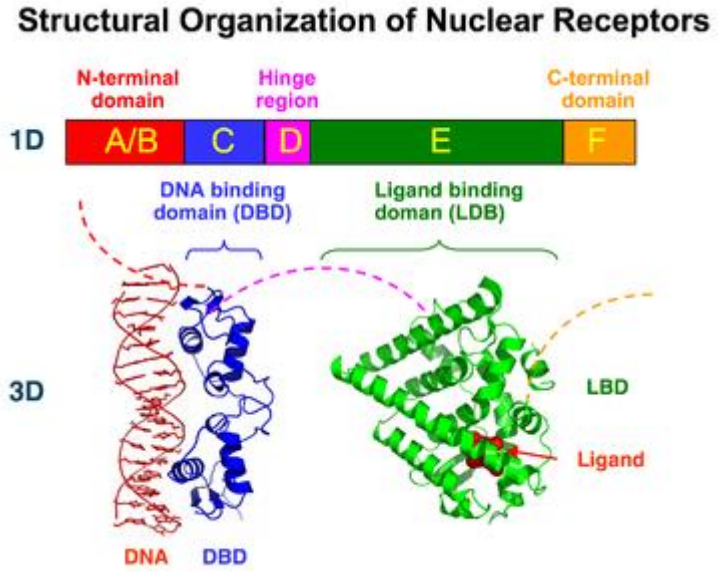
- Steroid hormone receptors are proteins that have a binding site for a particular steroid molecule.
- Steroid hormone receptors are found in the cytosol and also in the nucleus of target cells.
- Steroid hormone receptor belong to **NUCLEAR RECEPTOR FAMILY**.
- They are ligand-activated proteins that regulate transcription of selected genes.
- Their response elements are DNA sequences that are bound by the Hormone-Receptor complex.

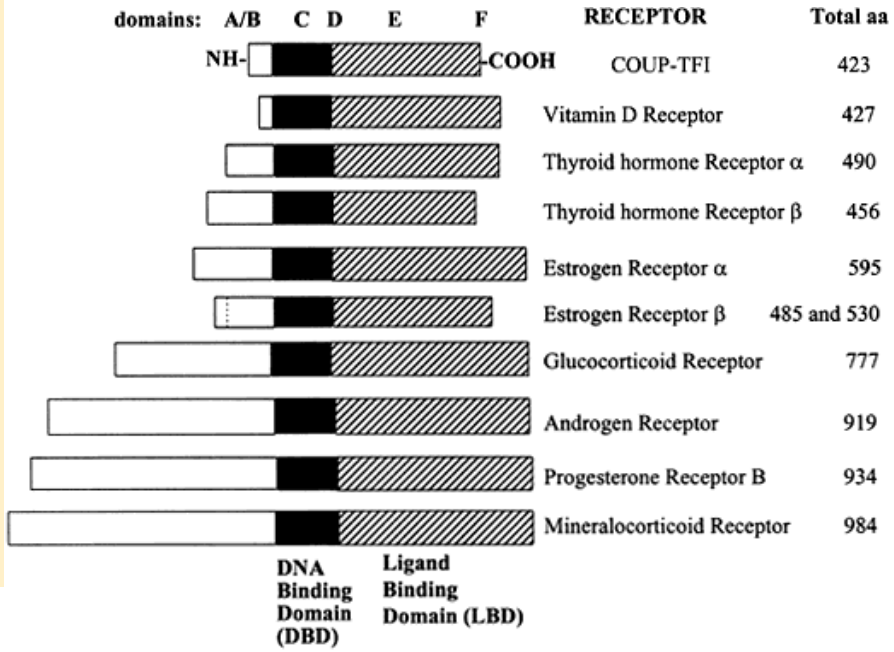
MOLECULAR STRUCTURE OF SHR

- The molecular structure of SHR shows presence of five distinct regions :
- Two end terminals – N terminal & C terminal.
- A hinge region
- Two domains – DNA binding domain & Ligand binding domain.



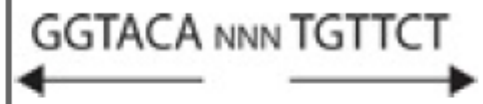
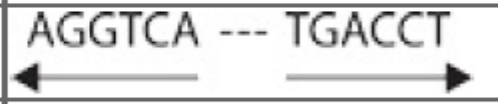
DIAGRRAMATIC REPRESENTATION OF SRUCTURE OF SHR





Structure of steroid hormone receptor:

- molecular masses between 50,000 and 100,000 daltons.
- Nuclear receptors are modular in structure and contain the following domains:
- **(A-B)** N-terminal regulatory domain: Contains **the activation function 1** (**AF-1**) whose action is independent of the presence of ligand. The transcriptional activation of AF-1 is normally very weak, but it does synergize with AF-2 in the E-domain to produce a more robust upregulation of gene expression. The A-B domain is highly variable in sequence between various nuclear receptors.
- **(C)** DNA-binding domain (**DBD**): Highly conserved domain containing two zinc fingers that binds to specific sequences of DNA called hormone response elements (HRE).
- **(D) Hinge region**: Thought to be a flexible domain that connects the DBD with the LBD. Influences intracellular trafficking and subcellular distribution.
- **(E) Ligand binding domain** (**LBD**): Moderately conserved in sequence and highly conserved in structure between the various nuclear receptors. The structure of the LBD is referred to as an **alpha helical** sandwich fold in which three anti parallel alpha helices (the "sandwich filling") are flanked by two alpha helices on one side and three on the other (the "bread"). The ligand binding cavity is within the interior of the LBD and just below three anti parallel alpha helical sandwich "filling". Along with the DBD, the LBD contributes to the **dimerization** interface of the receptor and in addition, **binds coactivator and corepressor proteins**. The LBD also contains the activation function 2 (**AF-2**) whose action is dependent on the presence of bound ligand.
- **(F)** C-terminal domain: Highly variable in sequence between various nuclear receptors.
- The N-terminal (A/B), DNA-binding (C), and ligand binding (E) domains are independently well folded and structurally stable while the hinge region (D) and optional C-terminal (F) domains may be conformationally flexible and disordered

Hormone or Effector	HRE	DNA Sequence
Glucocorticoids	GRE	
Progestins	PRE	
Mineralocorticoids	MRE	
Androgens	ARE	
Estrogens	ERE	
Thyroid hormone	TRE	
Retinoic acid	RARE	
Vitamin D	VDRE	
cAMP	CRE	TGACGTCA

1. Arrows = inverted palindrome sequences
2. "half binding sites," or half-sites, because each binds one monomer of the receptor
3. GRE, PRE, MRE, and ARE consist of the same DNA sequence. For this, intracellular concentration of the ligand or receptor, flanking DNA sequences & other accessory elements determine specificity.
4. TRE (N=4), RARE (N=5) & VDRE (N =3) – differ by orientation and spacing between the half palindromes
5. Retinoid X receptor (RXR), forms heterodimers with VDR, TR, and RARE.

At a glance!!!!!

GROUP I HORMONES	GROUP II HORMONES
Steroid hormones, peptide hormones like thyroxin, vitamins like retinoid (Vit A), calcitriol (vit D)	Peptide hormones (except thyroxin)
Intracellular receptors (nuclear receptors for thyroxin & retinoids; cytoplasmic receptors for steroids)	Transmembrane receptors (cell membrane)
Directly binds to DNA via DNA-binding domain of the receptor.	Acts by any one of the following four mechanisms: (1) Secondary messengers (cAMP) (2) Receptor kinase (Tyr-kinase) (3) Membrane potential (4) Adhesion receptor
Found in free (biologically active) form or bound form (bound to transport/carrier proteins)	Found in only free forms.
Longer half-life due to low metabolism	Shorter half-life