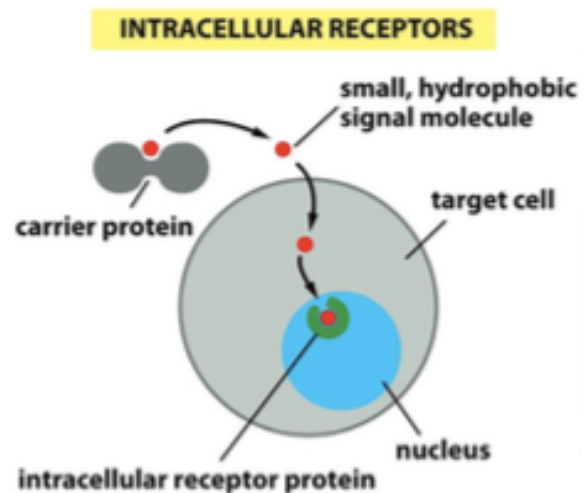


LECTURE B3

Hormones can be divided into two groups:

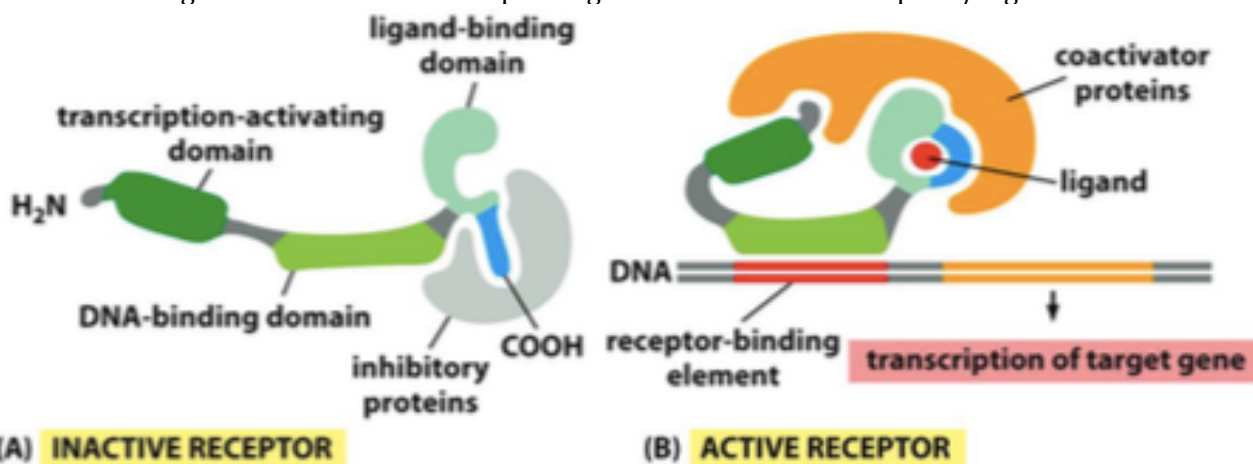
1. Act via cell **surface receptors**, do not enter cell and initiate intracellular signalling pathways
2. Hormones that enter the cell, lipophilic and target an **intracellular receptor** – the **nuclear receptors**

**Intracellular nuclear receptors**

- Mediate signals from **lipophilic ligands** (hormones) to the **nucleus** of cells to alter gene expression and eventually physiology
- Hormones must be able to cross the lipid bilayer via passive diffusion to access receptor
- Many nuclear receptors function as ligand-dependent **transcriptional regulators** (one stop signalling molecule) that regulate gene transcription by binding genes
- Main **functional roles** in reproduction, integrated metabolism and homeostasis

Nuclear receptors

- Have 3 key domains: a ligand binding domain, a DNA binding domain and a transcription activating domain (interacts with proteins)
- Other domains interact with transcription proteins
- Nuclear receptors are bound by chaperones such as inhibitory proteins that fall off and move to nucleus via nucleolocalisation stretch during activation due to conformational changes
- 3D changes move the COOH to trap the ligand for nuclear transcription/regulation



- Ligand-activated receptors (some are inside cell, some are on the DNA) mostly **activate gene transcription**, repression is a characteristic of the apo-nuclear receptor (no ligand)
- Examples include steroids (testosterone, estradiol, cortisol) and vitamin D
- Excess of cortisol results in **cushings syndrome** which can be treated by antagonist RU486

Steroid biosynthesis

- This occurs in cells within the **adrenal cortex** via many enzyme biosynthesis pathways
- A range of diseases are caused by mutations in the genes for these enzymes
- Abnormalities are usually present in early childhood and treatment includes steroid hormone replacement

Mechanism of action for nuclear receptors

- Nuclear receptors can reside in the cytoplasm and/or nucleus
- Ligand precursor is activated/modified before binding to receptor inside the cell
- Ligand binding induces dimerization and binding to DNA on hormone responsive genes
- 3D changes cause the binding or co-activators such as **helix 12**