



RECEPTOR MECHANISMS

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Receptor

The component of a cell or organism that interacts with a drug and initiates the chain of biochemical events leading to the drug's observed effects.

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Signaling mechanisms

- 1) Lipid soluble ligand and intracellular nuclear receptor.
- 2) Transmembrane receptor and intracellular enzymatic activity.
- 3) Transmembrane receptor and tyrosine kinase activity.
- 4) Ligand gated transmembrane ion channel.
- 5) Transmembrane receptor and G protein.

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Nuclear receptors

- Corticosteroids, mineralocorticoids, sex steroids, vitamin D and thyroid hormone.
- Stimulate the transcription of genes in the nucleus by binding to specific DNA sequences.
- Produce their effects after a lag period of 30 minutes to several hours.
- Effect persists for hours or days after agonist conc. has reduced to 0.

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Transmembrane receptors with tyrosine kinase activity.

- Insulin, epidermal growth factor, platelet-derived growth factor, transforming growth factor- beta, atrial natriuretic peptide.
- Resulting change in receptor conformation causes receptor molecules to bind to one another.
- Tyrosine kinase domains come together and phosphorylate a number of proteins.

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Cytokine receptors

- Growth hormone, erythropoietin, interferons.
- Tyrosine kinase activity is not intrinsic to the receptor molecule. Separate protein tyrosine kinase from the **JANUS-KINASE** family binds non covalently to the receptor.

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Ligand-gated channels

- Acetylcholine, serotonin, GABA, glycine, aspartate, glutamate etc.
- Time elapsed between binding of agonist and the cellular response is generally in milliseconds.

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G proteins and second messengers

- “Serpentine” or “seven-transmembrane” receptors.
- Catecholamines, FSH, angiotensin, glucagon, vasopressin, parathyroid, LH, platelet activating factor, prostacyclin.

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Well established second messengers

- 1) cAMP-cyclic adenosine monophosphate
- 2) Calcium and Phosphoinositides
- 3) cGMP-cyclic guanosine monophosphate

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Ligand	Second messenger
Beta-adrenoceptors	cAMP
FSH	cAMP
Ach muscarinic receptors	Ca ²⁺ , phosphoinositides
Vasopressin	Ca ²⁺ , phosphoinositides
ANP	cGMP

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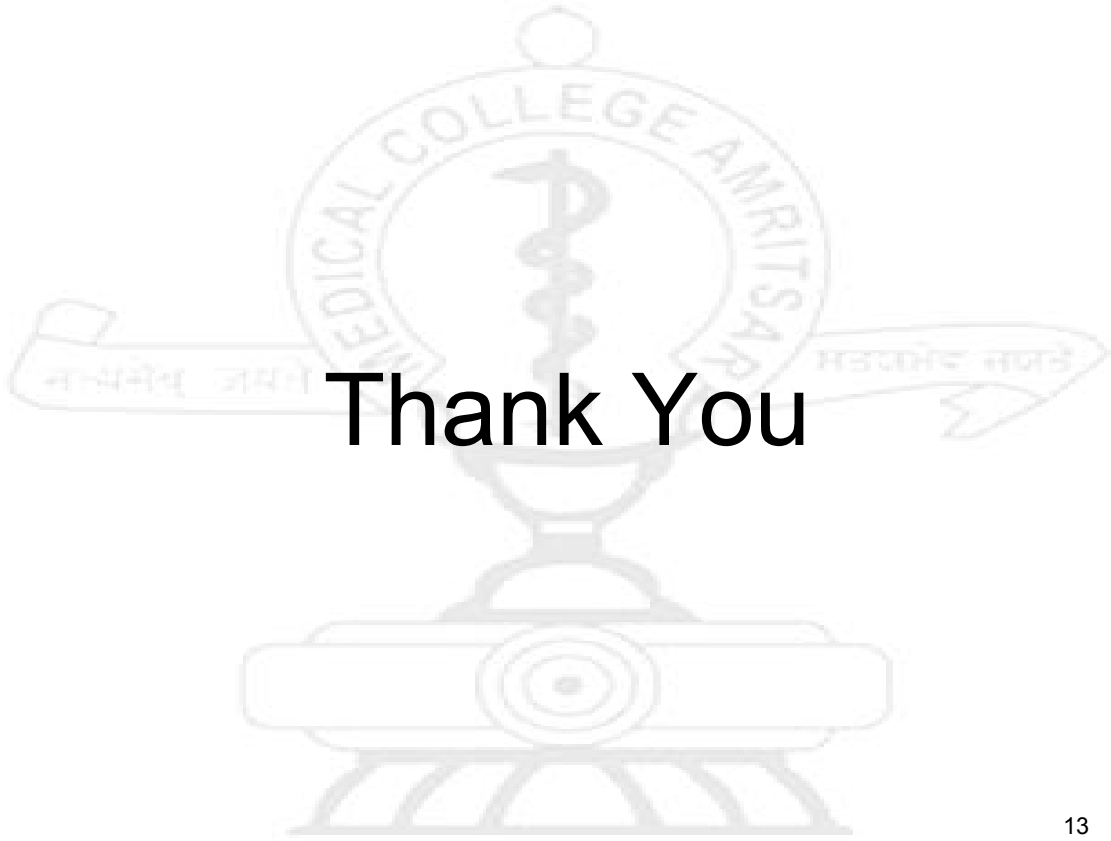
Receptor regulation

- 1) **Desensitization** – Receptor mediated response to drugs often desensitize with time. After reaching an initial high level, the response gradually diminishes over seconds or minutes, even in the continued presence of the agonist.
 - Agonist – receptor – stimulate BARK (beta adrenoceptor kinase) – Beta arrestin – decreased agonist response.
 - Rapid response

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- 2) **Downregulation** decreases the actual number of receptors present in the cell or tissue.
 - Slow process and less reversible.
 - Ligand gated endocytosis and delivery to lysosomes.

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Thank You