Pharmacodynamics

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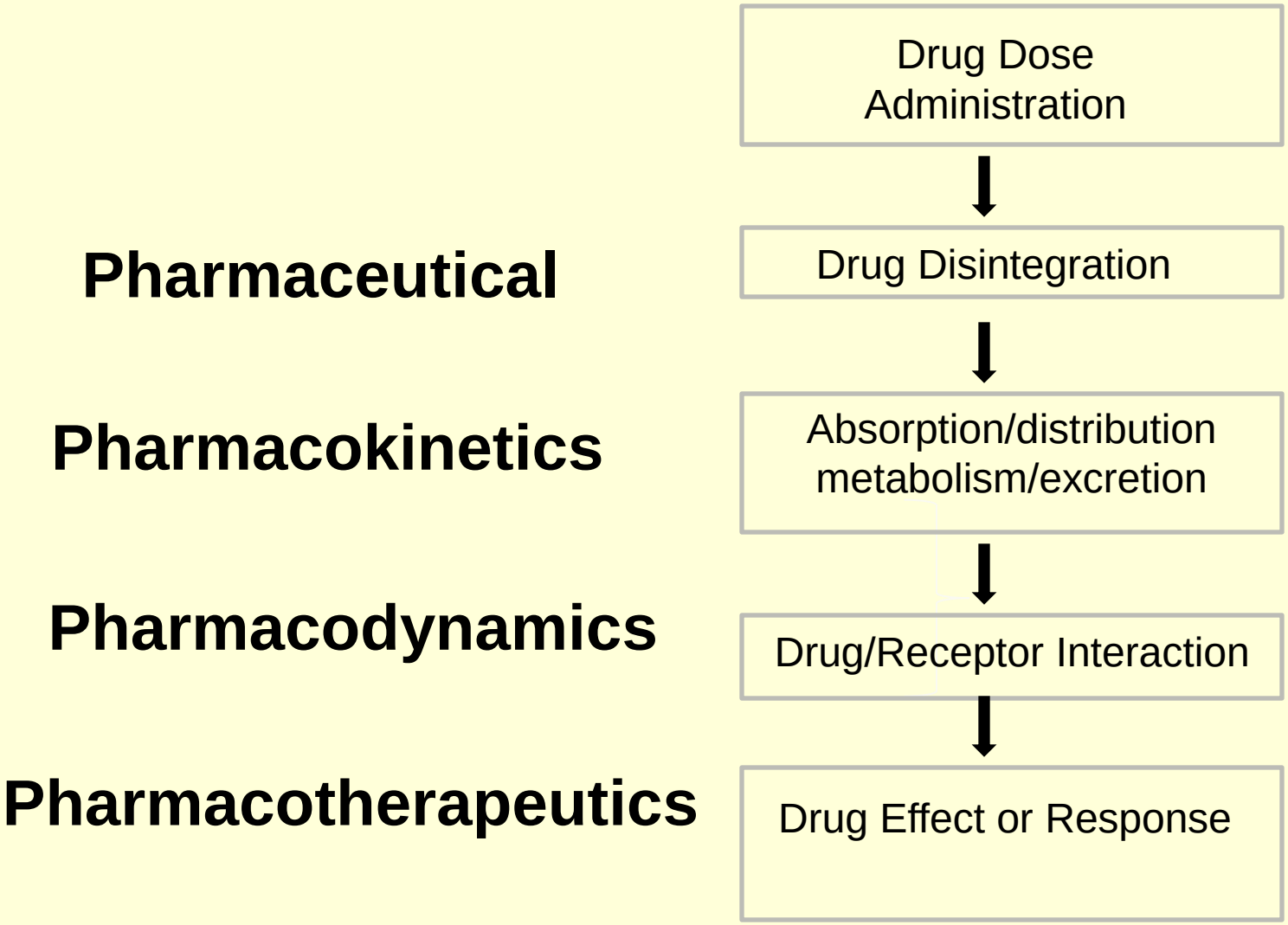
General Concepts



Pharmacodynamics

The action of a drug on the body, including receptor interactions, dose-response phenomena, and mechanisms of therapeutic and toxic action.

Study of the biochemical and physiologic effects of drugs and their mechanisms of action.

Receptor is any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes, nucleic acids, and structural proteins can act as receptors for drugs or endogenous agonists.

The drug–receptor complex

Cells have many different types of receptors, each of which is specific for a particular agonist and produces a unique response. Cardiac cell membranes, for example, contain β receptors that bind and respond to epinephrine or norepinephrine, as well as muscarinic receptors specific for acetylcholine. These different receptor populations dynamically interact to control the heart's vital functions. The magnitude of the response is proportional to the number of drug– receptor complexes.

The drug–receptor complex

This concept same as: enzyme and substrate or antigen and antibody.

Most receptors are named for the type of their agonist. For example, the receptor for histamine is called a histamine receptor.

Not all drugs exert their effects by interacting with receptors, e.g. Antacids, chemically neutralize excess gastric acid.

Receptor states

Receptors exist in two states: inactive (R) and active (R*), that are in reversible equilibrium with one another.

Agonists causes the equilibrium to shift from R to R* to produce a biologic effect.

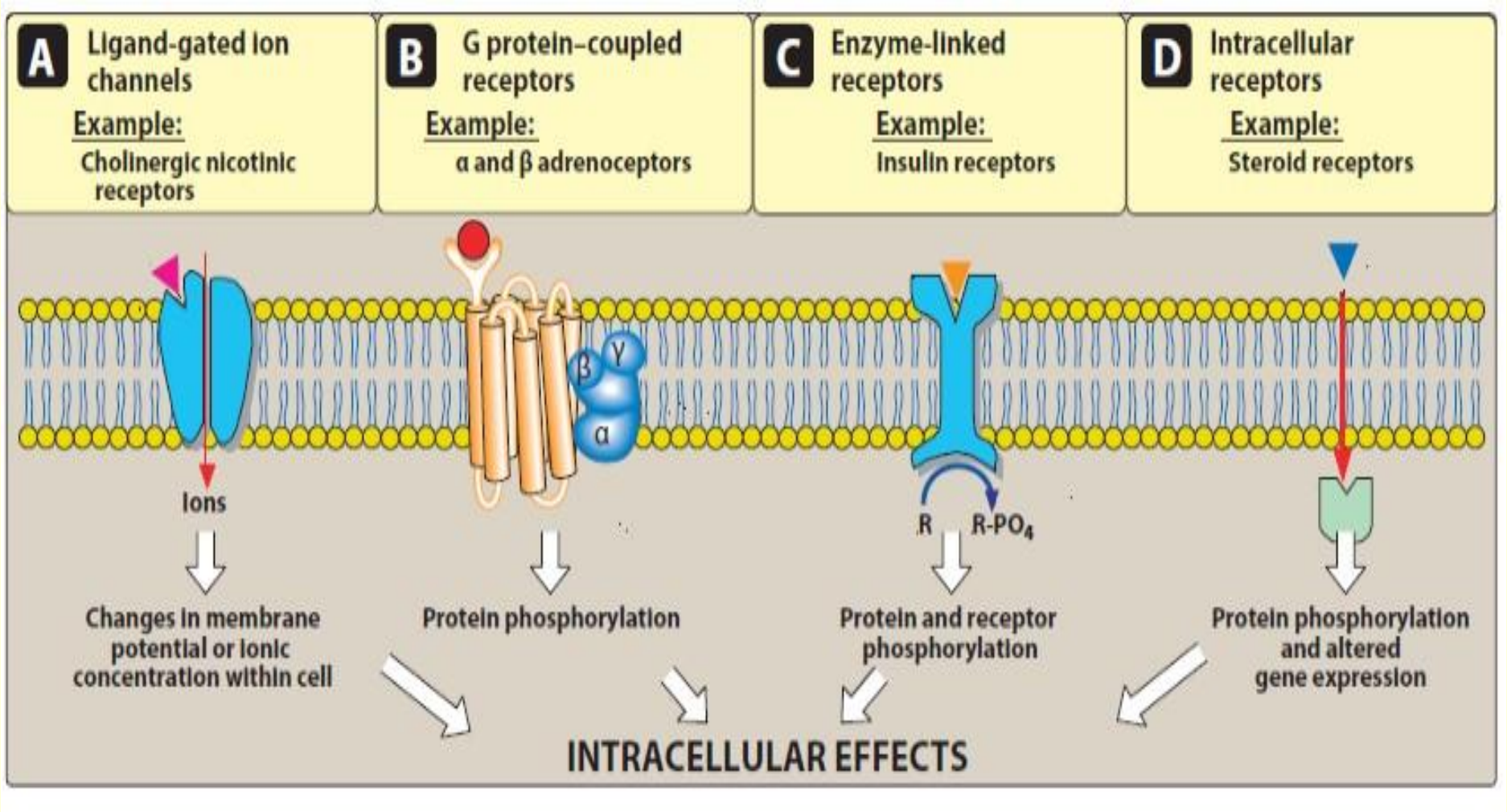
Antagonists occupy the receptor but do not increase the fraction of R* and may stabilize the inactive state.

Partial agonists causes the equilibrium to shift from R to R* but the R* is less than caused by an agonist and more than that caused by an antagonist.

The biological effect is directly related to the fraction of R*.

Major receptor families

Receptors are divided into four families:



Major receptor families

The type of receptor a ligand interacts with depends on the chemical nature of the ligand.

Hydrophilic ligands interact with receptors that are found on the cell surface.

In contrast, **hydrophobic ligands** enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells.

Transmembrane ligand-gated ion channels

The extracellular portion contains the ligand binding site.

The channel is closed until the receptor is activated by an agonist, which opens the channel for a few milliseconds.

These receptors mediate diverse functions, including neurotransmission, and cardiac or muscle contraction.

For example, stimulation of the nicotinic receptor by acetylcholine results in sodium influx and potassium outflux, generating an action potential in a neuron or contraction in skeletal muscle.

Transmembrane ligand-gated ion channels

On the other hand, agonist stimulation of the γ-aminobutyric acid (GABA) receptor increases chloride influx and hyperpolarization of neurons.

Voltage-gated ion channels may also possess ligand-binding sites that can regulate channel function. For example, local anesthetics bind to the voltage- Gated sodium channel, inhibiting sodium influx and decreasing neuronal conduction.

Transmembrane G protein–coupled receptors

The extracellular domain of this receptor contains the ligand-binding area, and the intracellular domain interacts (when activated) with a G protein or effector molecule.

There are many kinds of G proteins (for example, Gs, Gi, and Gq), but they all are composed of three protein subunits. The α subunit binds guanosine triphosphate (GTP), and the β and γ subunits anchor the G protein in the cell membrane.

Transmembrane G protein–coupled receptors

Binding of an agonist to the receptor increases GTP binding to the α subunit, causing dissociation of the α-GTP complex from the βγ complex. These two complexes can then interact with other cellular effectors, usually an enzyme, a protein, or an ion channel, that are responsible for further actions within the cell. These responses usually last several seconds to minutes.

Sometimes, the activated effectors produce second messengers that further activate other effectors in the cell, causing a signal cascade effect.

Transmembrane G protein–coupled receptors

A common effector, activated by Gs and inhibited by Gi, is adenylyl cyclase, which produces the second messenger cyclic adenosine monophosphate (cAMP).

Gq activates phospholipase C, generating two other second messengers: inositol trisphosphate (IP3) and diacylglycerol (DAG). DAG and cAMP activate different protein kinases within the cell, leading to a myriad of physiological effects.

IP3 regulates intracellular free calcium concentrations, as well as some protein kinases.

Enzyme-linked receptors

These receptors consists of a protein that form dimers or multisubunit complexes. When activated, these receptors undergo conformational changes resulting in increased cytosolic enzyme activity. This response lasts minutes to hours.

The most common receptors (epidermal growth factor, platelet-derived growth factor, insulin, and others) possess tyrosine kinase activity as part of their structure.

The activated receptor phosphorylates tyrosine residues on itself and then other specific proteins. Phosphorylation can modify the structure of the target protein.

Enzyme-linked receptors

For example, when the peptide hormone insulin binds to two of its receptor subunits, their intrinsic tyrosine kinase activity causes autophosphorylation of the receptor itself.

In turn, the phosphorylated receptor phosphorylates other peptides or proteins that subsequently activate other important cellular signals. This cascade of activations results in a multiplication of the initial signal, much like that with G protein– coupled receptors.

Intracellular receptors

The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular, and therefore, the ligand must diffuse into the cell to interact with the receptor. In order to move across the target cell membrane, the ligand must have sufficient lipid solubility. The primary targets of these ligand receptor complexes are transcription factors in the cell nucleus.

Binding of the ligand with its receptor generally activates the receptor via dissociation from a variety of binding proteins. The activated ligand–receptor complex then translocates to the nucleus, where it often dimerizes before binding to transcription factors that regulate gene expression.

Intracellular receptors

The activation or inactivation of these factors causes the transcription of DNA into RNA and translation of RNA into an array of proteins.

The time course of activation and response of these receptors is on the order of hours to days. For example, **steroid hormones** exert their action on target cells via intracellular receptors. Other targets of intracellular ligands are structural proteins, enzymes, RNA, and ribosomes. For example, **tubulin** is the target of antineoplastic agents such as paclitaxel , the enzyme **dihydrofolate reductase** is the target of antimicrobials such as trimethoprim and the **50S subunit** of the bacterial ribosome is the target of macrolide antibiotics such as erythromycin.

Mechanisms of Drug action

1. Through receptors (cell proteins) e.g. Cholinergic receptors occupied by acetylcholine. It is the most commonest way of drug action.

2. Through enzymes, either stimulating or inhibiting enzymes e.g. inhibition of cholinesterase enzyme by neostigmine.

3. Interference with ion channels e.g. blocking Na+-channels by local anaesthetics.

4. Inhibition of membrane bound enzymes e.g. Na+/K+ ATP-ase inhibition by digoxin.

Mechanisms of Drug action

5. Through physicochemical properties e.g. manitol acts as osmotic diuretic.

6. Direct chemical reaction e.g. Chelating agents in heavy metals poisoning.

7. Carrier mechanism: some drugs act by interfering with passage of molecules across the cell membrane such as the inhibition of noradrenalin uptake by tircyclic antidepressants.

Drug Receptor

- A macromolecular component of a cell with which a drug interacts to produce a response

- Usually a protein

Macromolecular nature of drug receptors

- Regulatory proteins
- Enzymes
- Transport proteins
- Structural proteins

Ligand gated ion channel (iontropic receptors)

Examples:

- γ-amino butyric acid (GABA)
- Glycine
- Aspartate
- Glutamate
- Acetylcholine
- Serotonin

G protein coupled receptors

Examples:

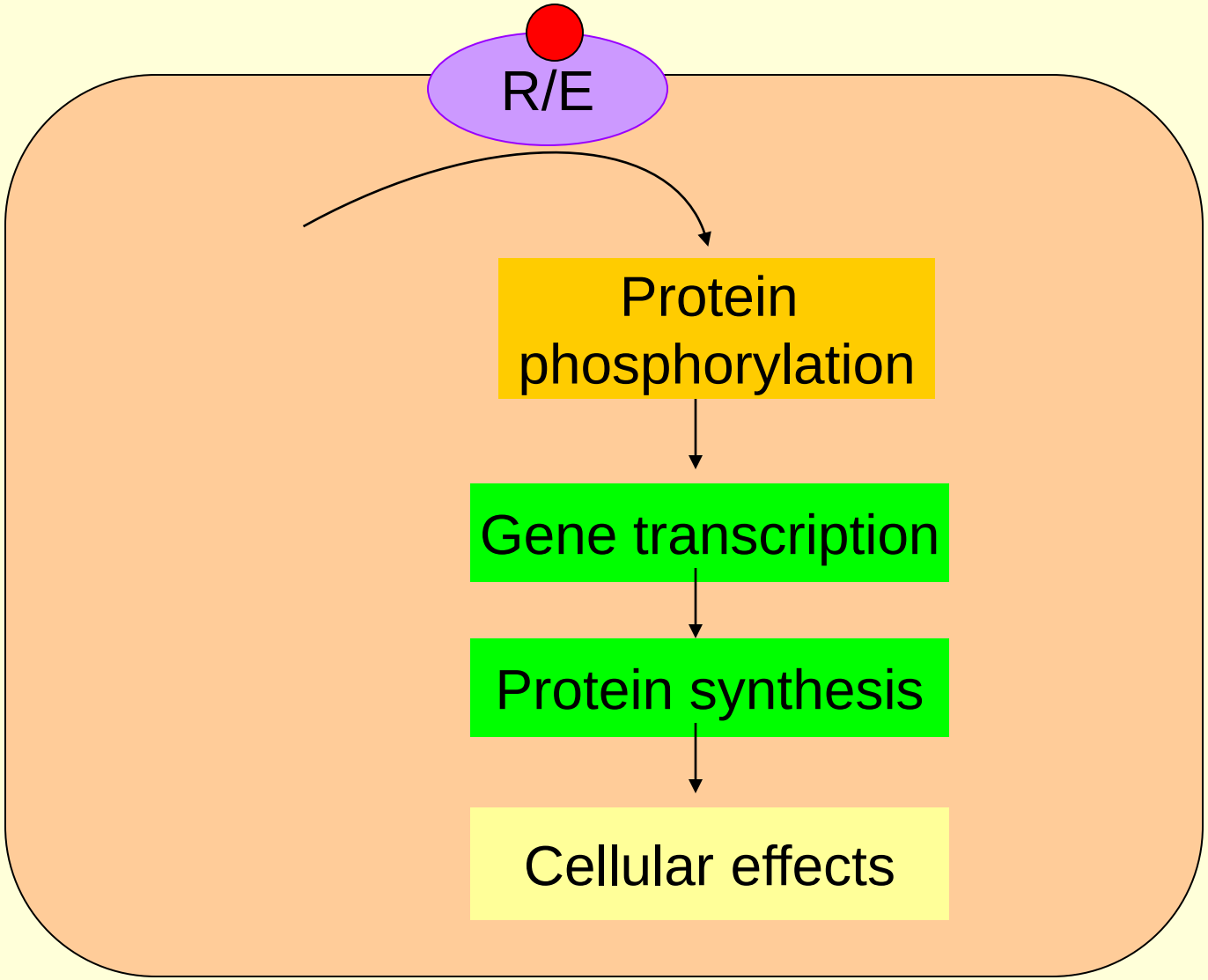
- Adernocorticotropic hormone
- Acetylcholine
- Angiotensine
- Catecholamines
- Chorionic gonadotropin
- Follicle stimulating hormone
- Glucagon
- Histamine
- Luteinizing Hormone
- Serotonin
- Vasopressin

Kinase linked receptors

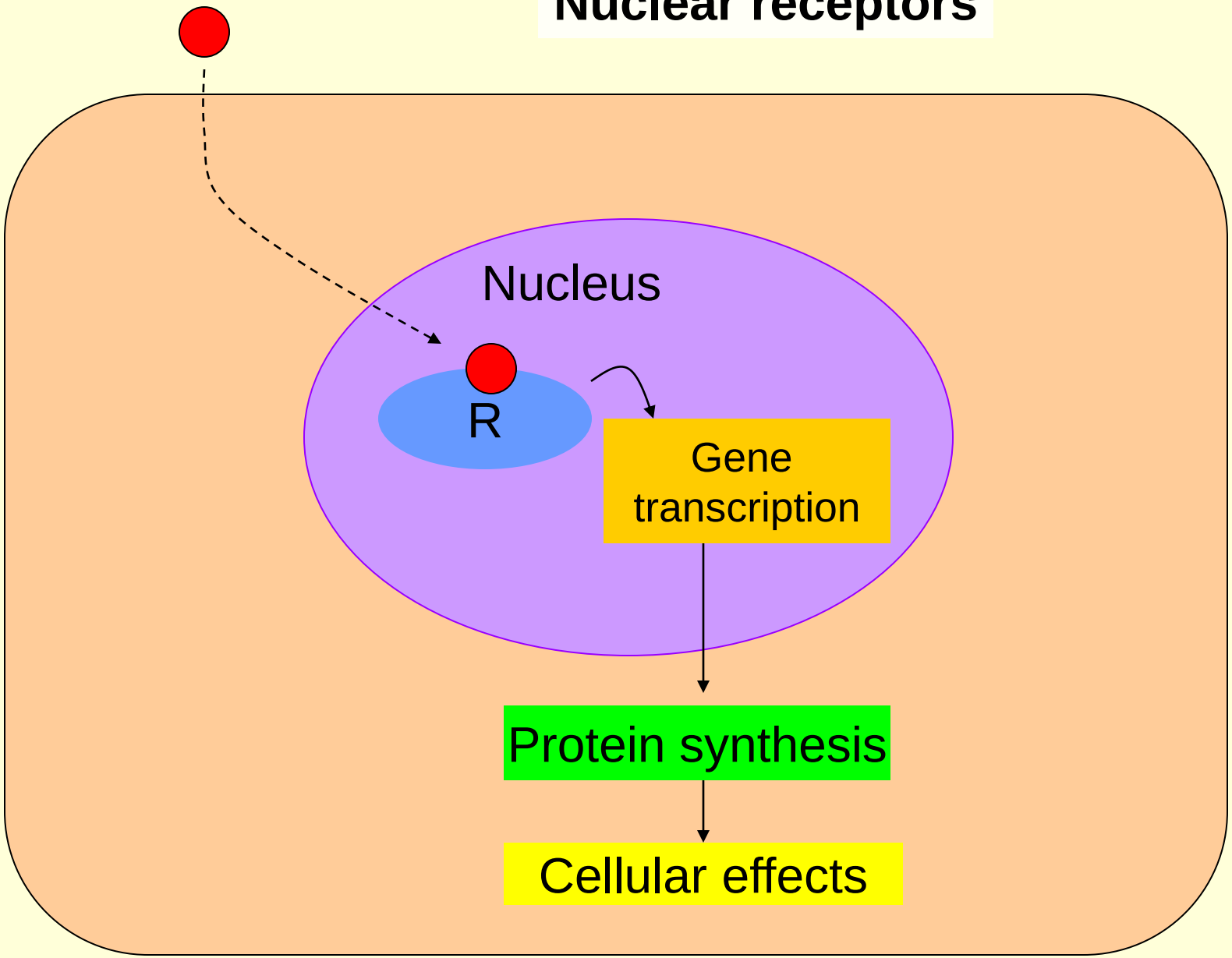
- **Ligand -regulated transmembrane enzyme including receptor tyrosine kinases**
  - Insulin
  - Epidermal growth factor (EGF)
  - Platelet-derived growth factor (PDGF)
  - Arterial natriuretic factor (ANF)
  - Transforming growth factor β(TGF- β)

- **Cytokine receptors**
  - Growth hormone
  - Erythropoietin
  - Interferones

Kinase linked receptors



Nuclear receptors



Second messenger

The second messenger is an intracellur component that can transmit the effect of the drug to the inside of the cell following receptor stimulation, E.g. c-AMP and calcium ions, changes in these second messenger will produce the drug effects as muscle contraction or relaxation or gland secretion.

Well Established Second Messengers

- Cyclic Adenosine Monophosphate (cAMP)
- Calcium and Phosphoinositides
- Cyclic Guanosine Monophosphate (cGMP)

Good Luck