كلية الطب البيطري – جامعة تكريت

ماجستير أدوية

أ د حسام الدين النجار

2024-2025 \ First Term

((5))

Advanced Pharmacology

Pharmacokinetic Principles

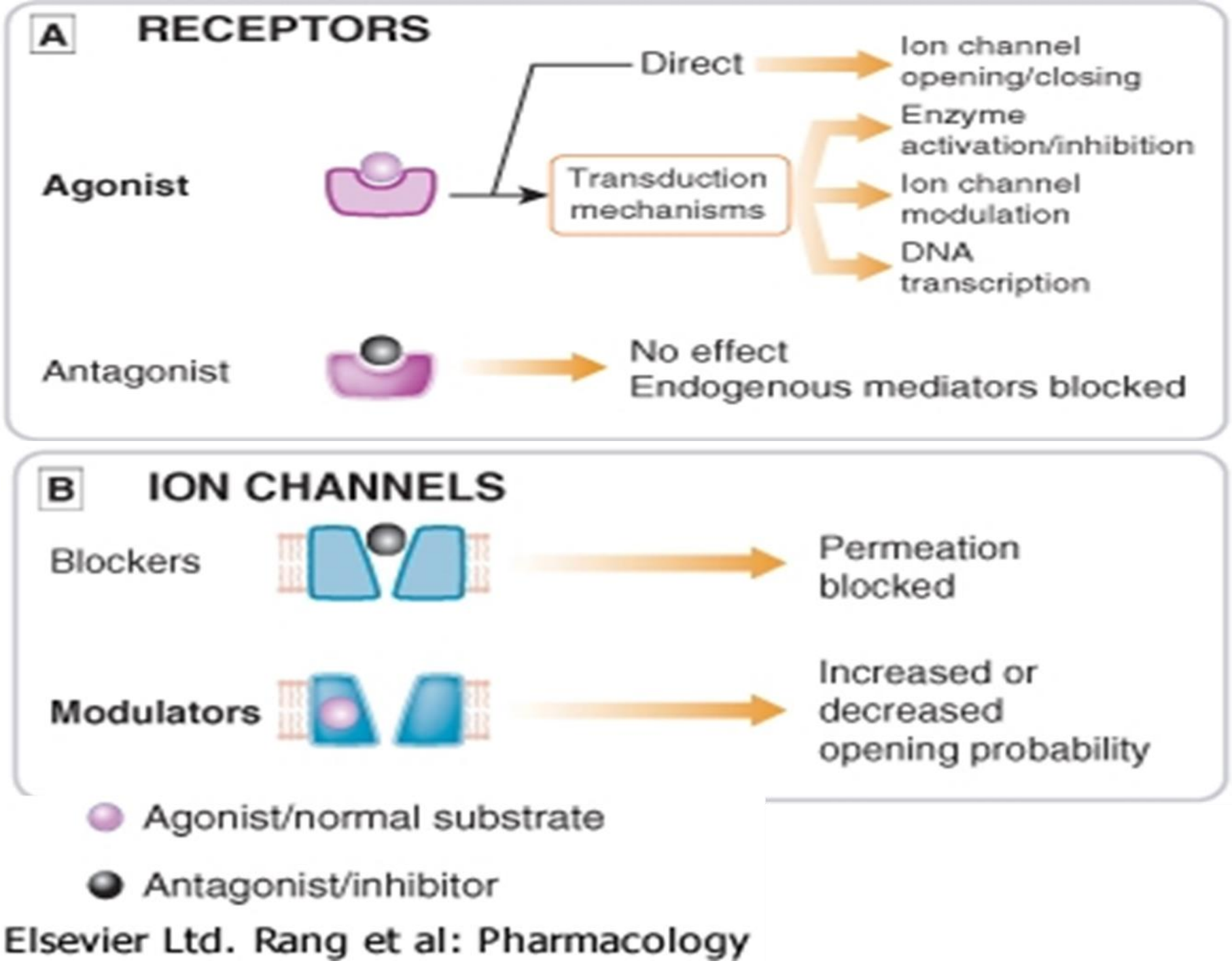
PHARMACODYNAMICS

د جسام الدين سالم النجار

How Drugs Act

Targets for drug Action

- **Protein Targets For Drug Binding:**
  1. *Regulatory Proteins*
  2. *Structural Proteins*



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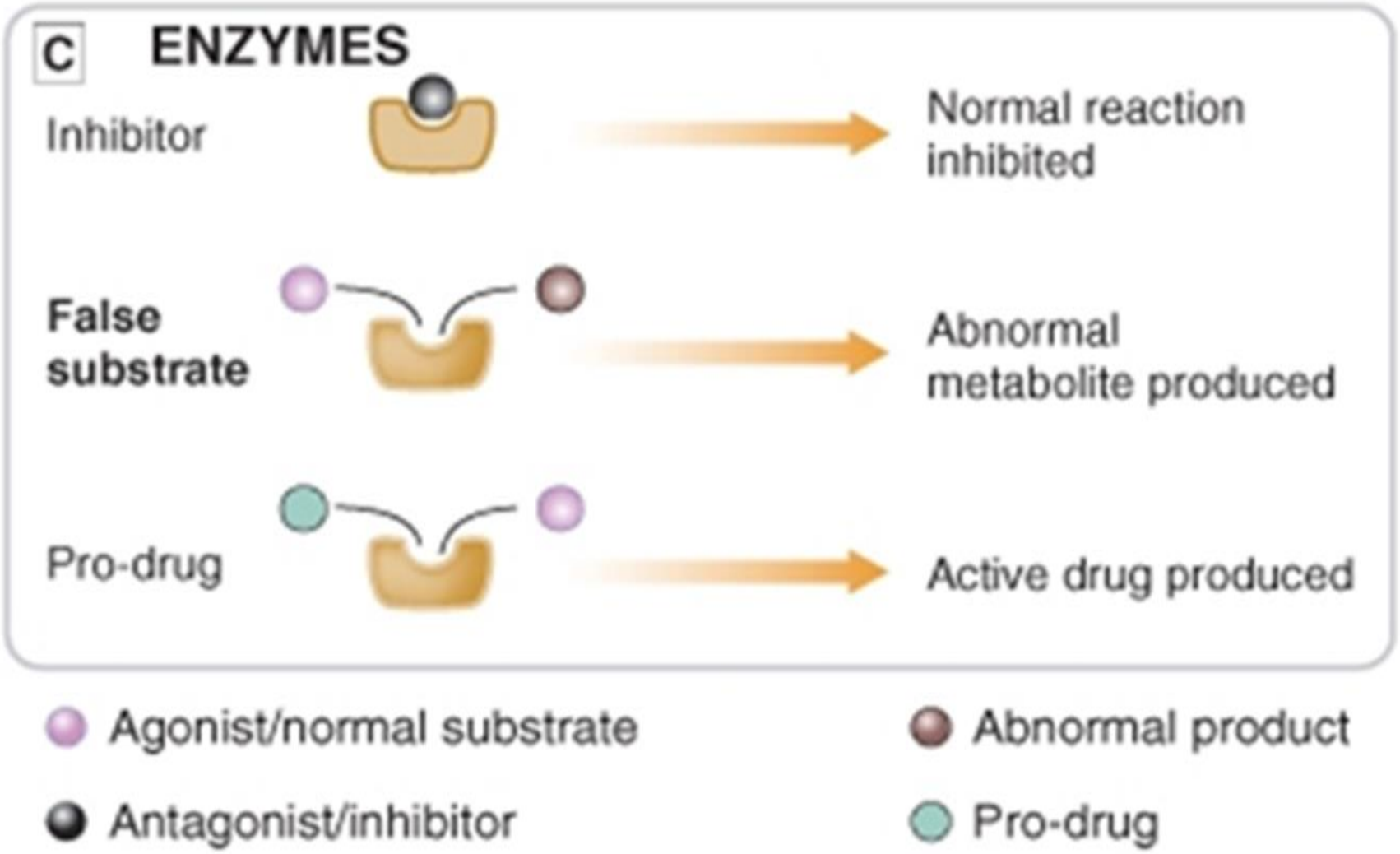

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- ***Regulatory Proteins:***

A. Receptors:

Are macromolecular proteins act as recognition sites for drugs (agonist or antagonist). They are functionally silent in the absence of the drug.

B. **Enzymes:**

1. **Competitive inhibitor:**

a. **Reversible**: neostigmine inhibits acetylcholinesterase, carbidopa inhibits dopa decarboxylase

b. Irreversible: aspirin inhibits COX

2. **False substrate** → abnormal product

(fluorouracil)

3. **Prodrug**: A parent compound lacks activity & needs enzymatic degradation to convert into the active form (cortisone & enalapril).

C. Carriers:

Transport of ions & organic molecules across cell membrane requires carriers.

- Loop diuretics block Na/K/2Cl co-transporter
- TCA & cocaine block N.A carrier (uptake1)
- cardiac glycosides block Na+ / K+ pump
- Omeprazole blocks proton pump.

D. Ion channels:

1. Ligand gated ion channel: gating is controlled by ligand binding
2. Voltage-gated ion channel: controlled by membrane potential.

- **Drug-channel binding**:

a. Direct: either Blockers (e.g local anesthetics block voltage-gated Na+ channel) or Modulators where the drug binds to an accessory site of the channel affecting gating (e.g. Ca^{2+} channel blockers inhibit opening of Ca^{2+} channel)

b. Indirect: involving G-protein

2. ***Structural proteins***:

- Colchicine interacts with tubulin.
- Ciclosporin acts on immunophilins.
- Therapeutic antibodies act against cytokines ,e.g. infliximab (anti-TNF-α antibody)

❑ ***Exceptions:***

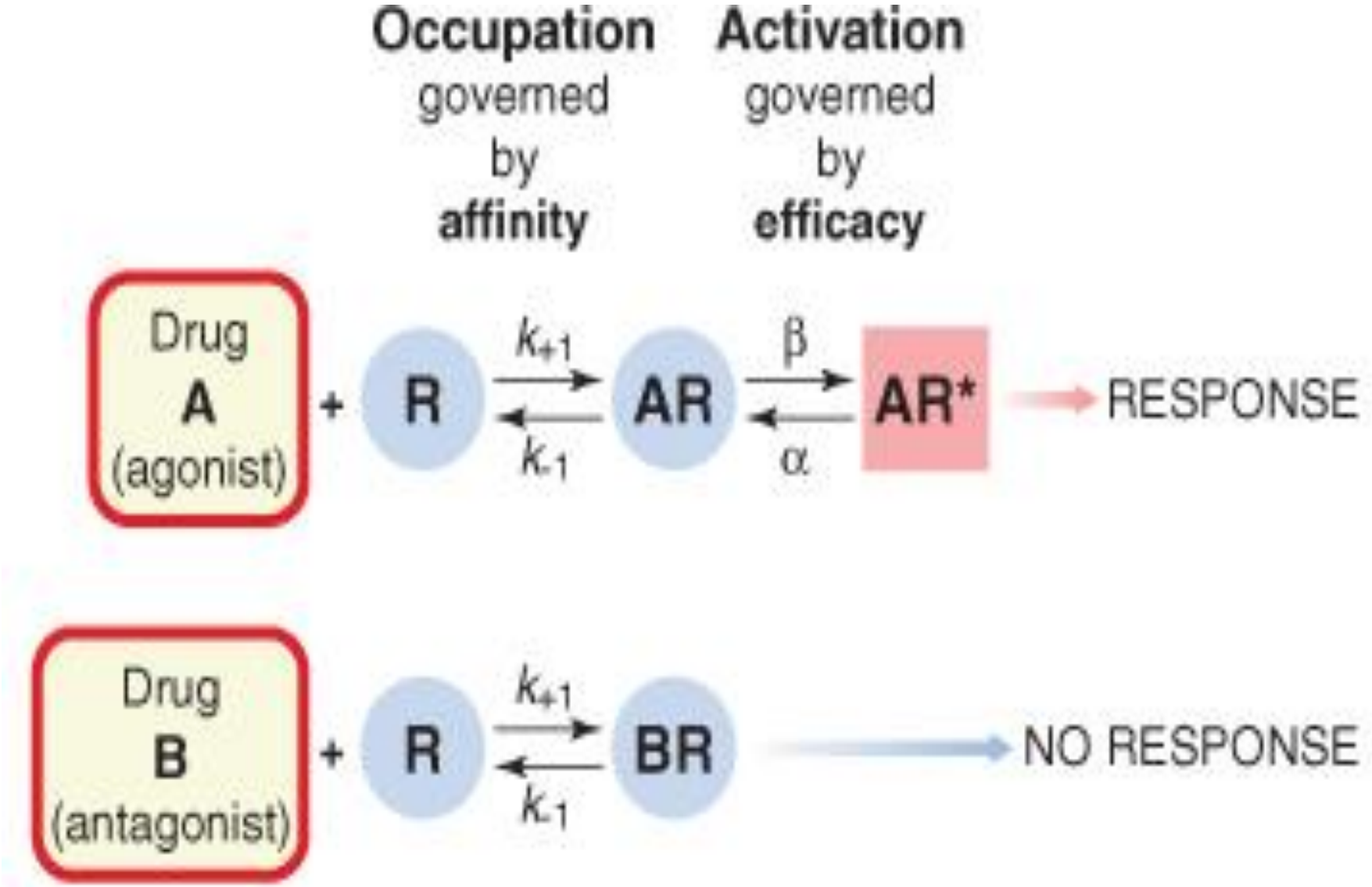
- Chemotherapeutic drugs:

  antimicrobial agents

  anticancers (interact directly with DNA).
- Some drugs produce their effect without binding to any cellular components, e.g. antacids, chelating drugs, osmotic diuretics & bulk laxatives.

Drug-Receptor interaction
Full & Partial agonist & antagonist

- Drug-Receptor binding may or may not result in receptor activation → response.
- Occupation → affinity (tendency of the drug to bind the receptor)
- Activation → efficacy (ability of a drug, once bound, to initiate changes → effect.



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- **Agonist**: a drug that binds to the receptor" affinity" → activation of the receptor" efficacy".

a. **Full agonist**: possesses ↑ affinity & efficacy (+1). Large % of receptors reside in (R*) → maximal tissue response

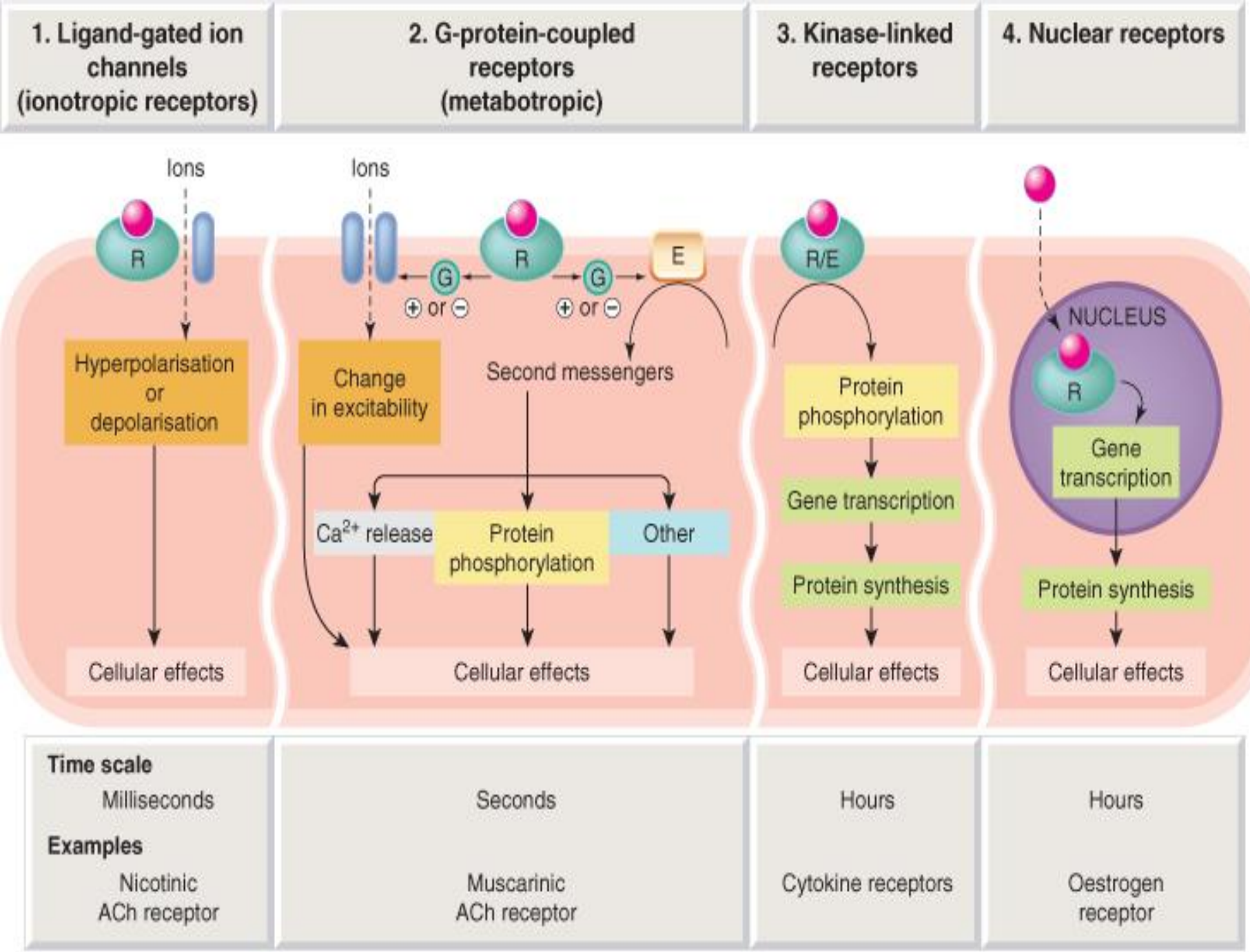
b. **Partial agonist**: possesses ↑ affinity & intermediate efficacy (0-1) i.e.↓ no. of receptors are activated even at 100% occupancy → submaximal tissue response.

   They have low intrinsic activity (act as an agonist, if no full agonist is present, or as antagonist if full agonist is present, e.g. Pindolol

- **Antagonist**: a drug that binds to the receptor " affinity" without causing activation " zero efficacy" i.e. equal affinity for (R) & (R*).

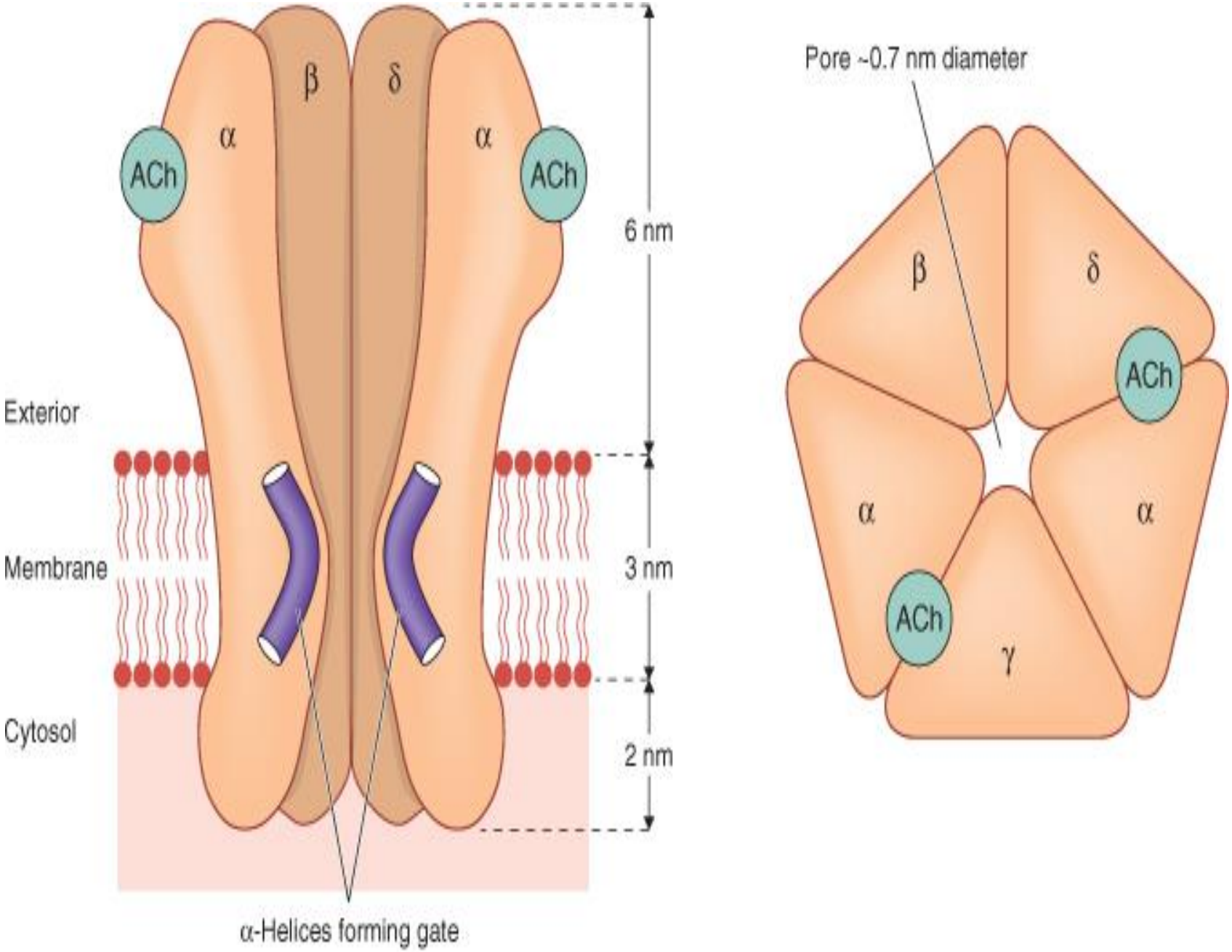
Receptor Families & Signaling Mechanisms

- Receptors link to a variety of cellular components (enzymes, ion channels…etc).
- The operation of this linkage is known as transduction mechanism.
- Four families of receptors are distinguished on the basis of their signaling mechanisms:



1. **Ion channel–linked receptor (inotropic):**

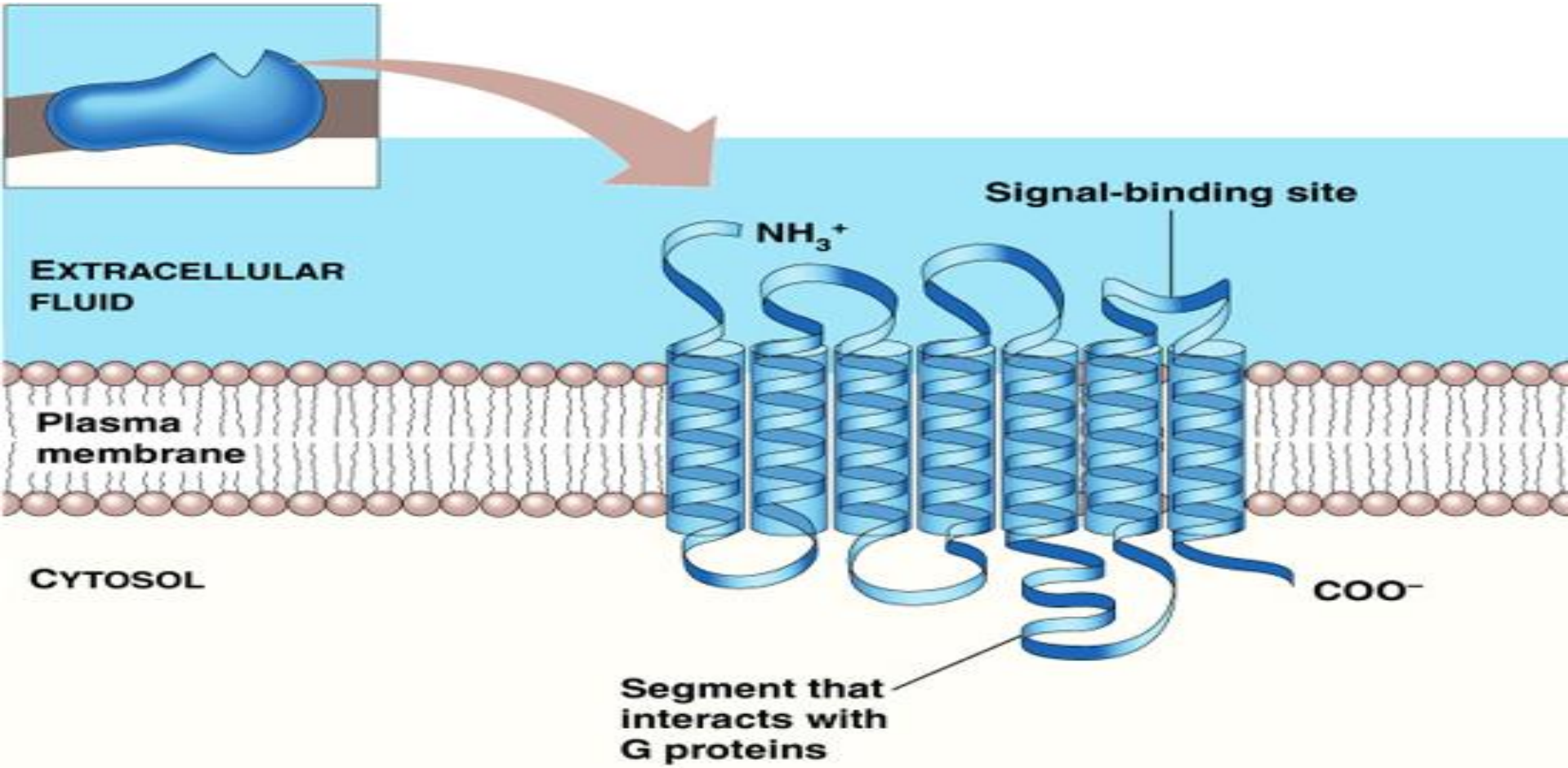
- Transmembrane receptor coupled directly to an ion channel, involved in fast neurotransmission.
- Transduction: millisecond.
- Ex. nAch, $GABA_A$, 5HT3 & glutamate receptors.
- nAch receptor: consists of 5 protein subunits (2α,β,ϒ,δ).
- Each subunit consists of polypeptide chain crosses the membrane 4 times (4 transmembrane helices).
- Gating mechanism: requires 2 molecules of Ach, conformational change, transient opening of the channel → Na+ influx.



2. G-protein coupled receptor (GPCR) (metabotropic):

- Transmembrane receptor coupled to intracellular effector systems via G-protein.
- Transduction: seconds. e.g. mAch, adrenergic, opiates, chemokines & dopamine receptors also odorant & visual receptors.
- Structure: A single polypeptide chain, comprises 7 transmembrane spanning segments (serpentine or heptahelical receptor).

STRUCTURE OF G-PROTEIN LINKED RECEPTOR



- **G-protein:** consists of (α,β,ϒ) trimer, with GDP or GTP binds α subunit. It interact with the third intracellular loop of the receptor.
- The family of G-proteins contain several subfamilies (with ↑ selectivity for a particular set of receptors and specific group of effectors) e.g. Gs, Gi, Go & Gq.

TABLE 2–1 G proteins and their receptors and effectors.

G Protein	Receptors for	Effector/Signaling Pathway
G_s	β-Adrenergic amines, glucagon, histamine, serotonin, and many other hormones	↑ Adenylyl cyclase → ↑ cAMP
G_{i1}, G_{i2}, G_{i3}	α_2-Adrenergic amines, acetylcholine (muscarinic), opioids, serotonin, and many others	Several, including: ↓ Adenylyl cyclase → ↓ cAMP Open cardiac K^+ channels → ↓ heart rate
G_{olf}	Odorants (olfactory epithelium)	↑ Adenylyl cyclase → ↑ cAMP
G_o	Neurotransmitters in brain (not yet specifically identified)	Not yet clear
G_q	Acetylcholine (muscarinic), bombesin, serotonin ($5\text{-}HT_{1C}$), and many others	↑ Phospholipase C → ↑ IP_3, diacylglycerol, cytoplasmic Ca^{2+}
G_{t1}, G_{t2}	Photons (rhodopsin and color opsins in retinal rod and cone cells)	↑ cGMP phosphodiesterase → ↓ cGMP (phototransduction)

cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate.