RECEPTORS:
Overview

Prof.Dr.Nuray ARI, 2018

TYPE of RECEPTORS

• Intracellular receptors: These are protein receptors that require the drug to cross the plasma membrane; therefore, the drug needs to be lipophilic. Steroids, for example, act by this mechanism.

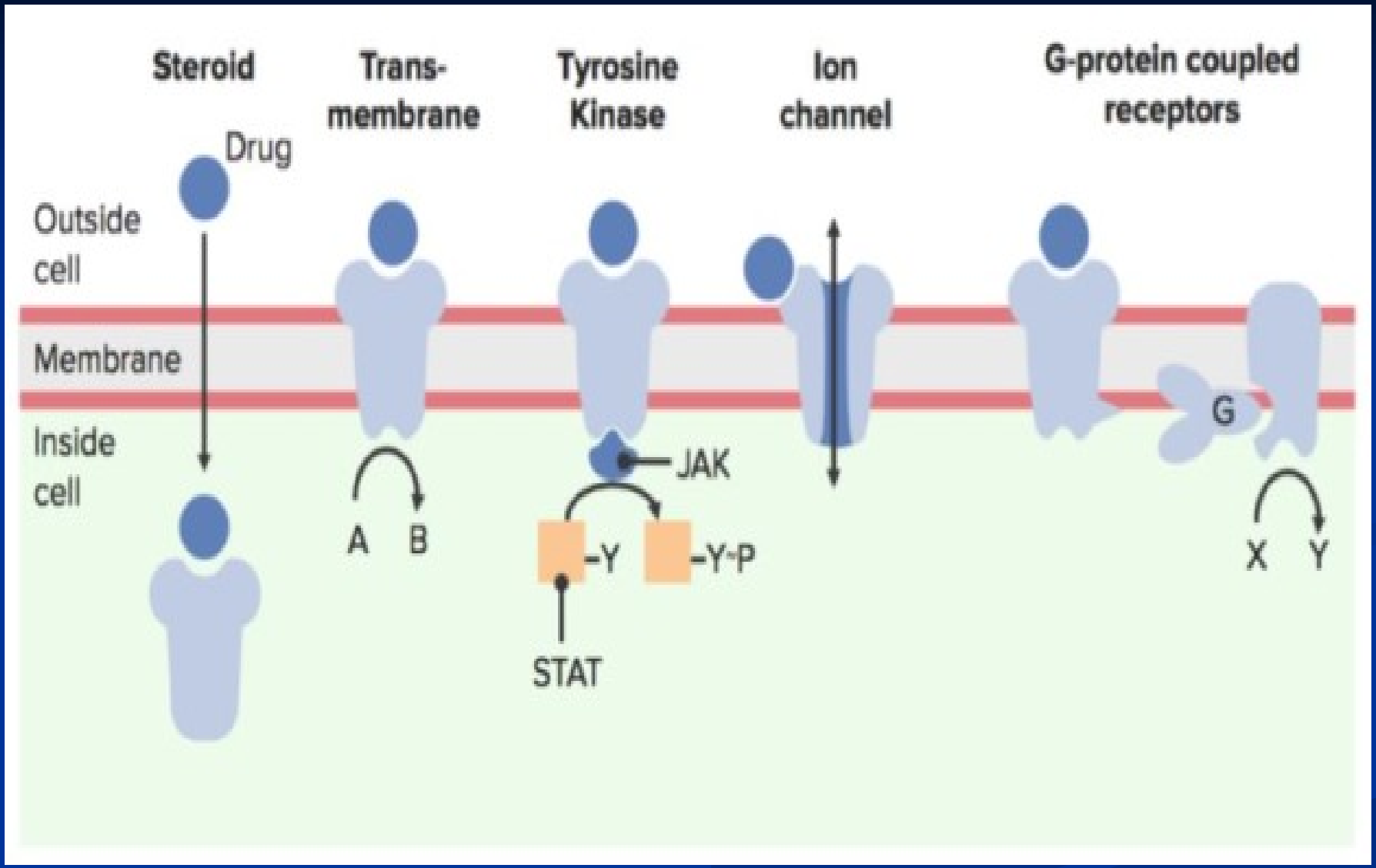
• Transmembrane enzymes: A drug binds to the extracellular component of this receptor, which activates an enzymatic reaction in the intracellular component.

Tyrosine kinase: When a drug binds to the extracellular component of this receptor, it leads to dimerizing of the two parts of the receptor intracellularly. This dimerization activates the tyrosine kinase enzymes, thereby leading to phosphorylation of tyrosine molecules on target proteins. Growth hormones and interferons act through JAK-STAT-kinase receptors.

• Ligand-gated ion channels: These ion channels are ligand-gated, i.e., they are closed until the receptor binds to the drug, which then allows specific ions to pass by. For example, drugs that stimulates GABA receptors on the neurons cause chloride influx (leading to hyperpolarization and thus, inhibition).

• G-protein coupled receptors: Similar to tyrosine kinase receptors, the drug-receptor binding leads to the interaction of the G-protein with the receptor. This activated G-protein then leads to the desired pharmacological response through one or a series of effector molecules or second messengers.

G-protein coupled receptors are common types of receptors in the body.



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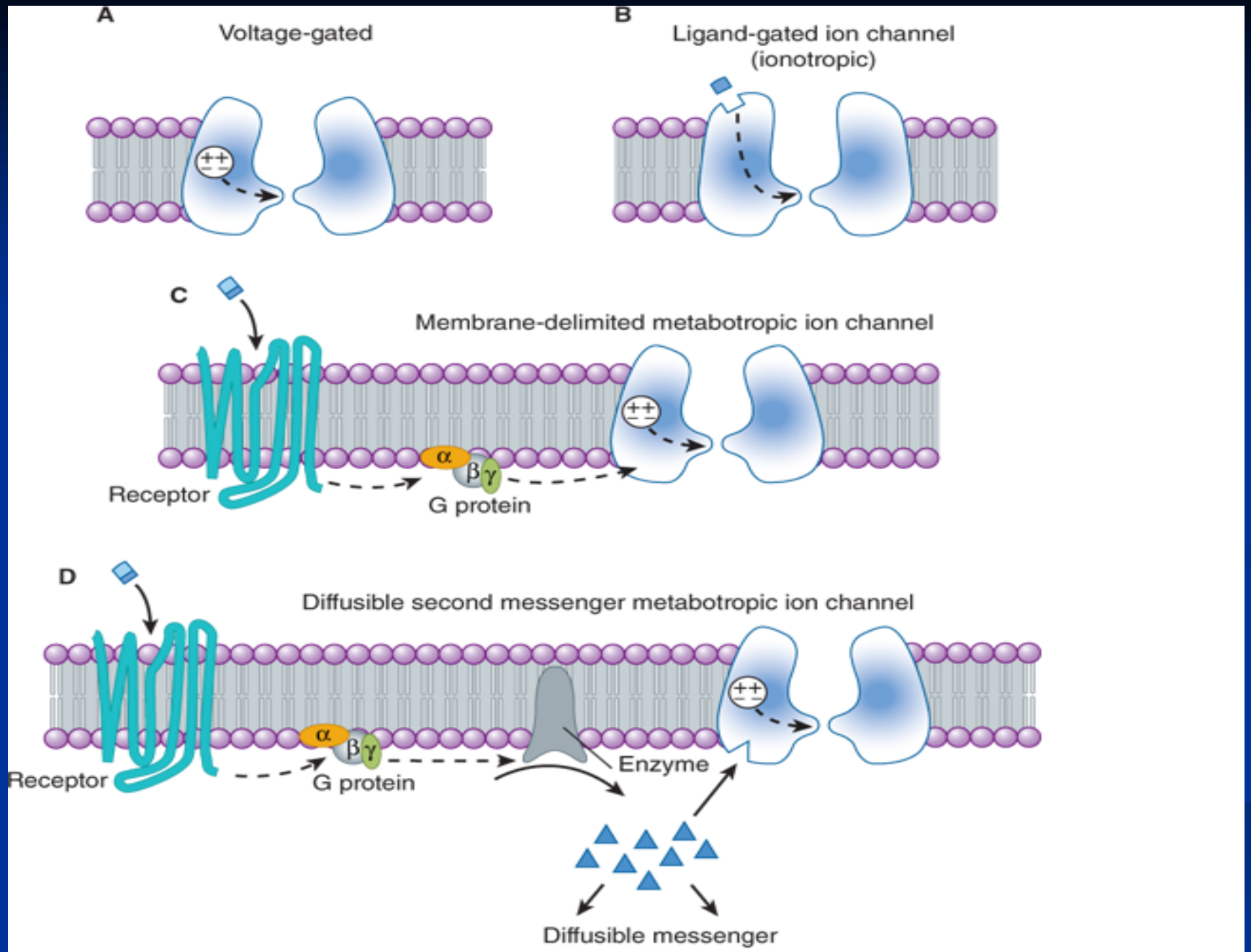
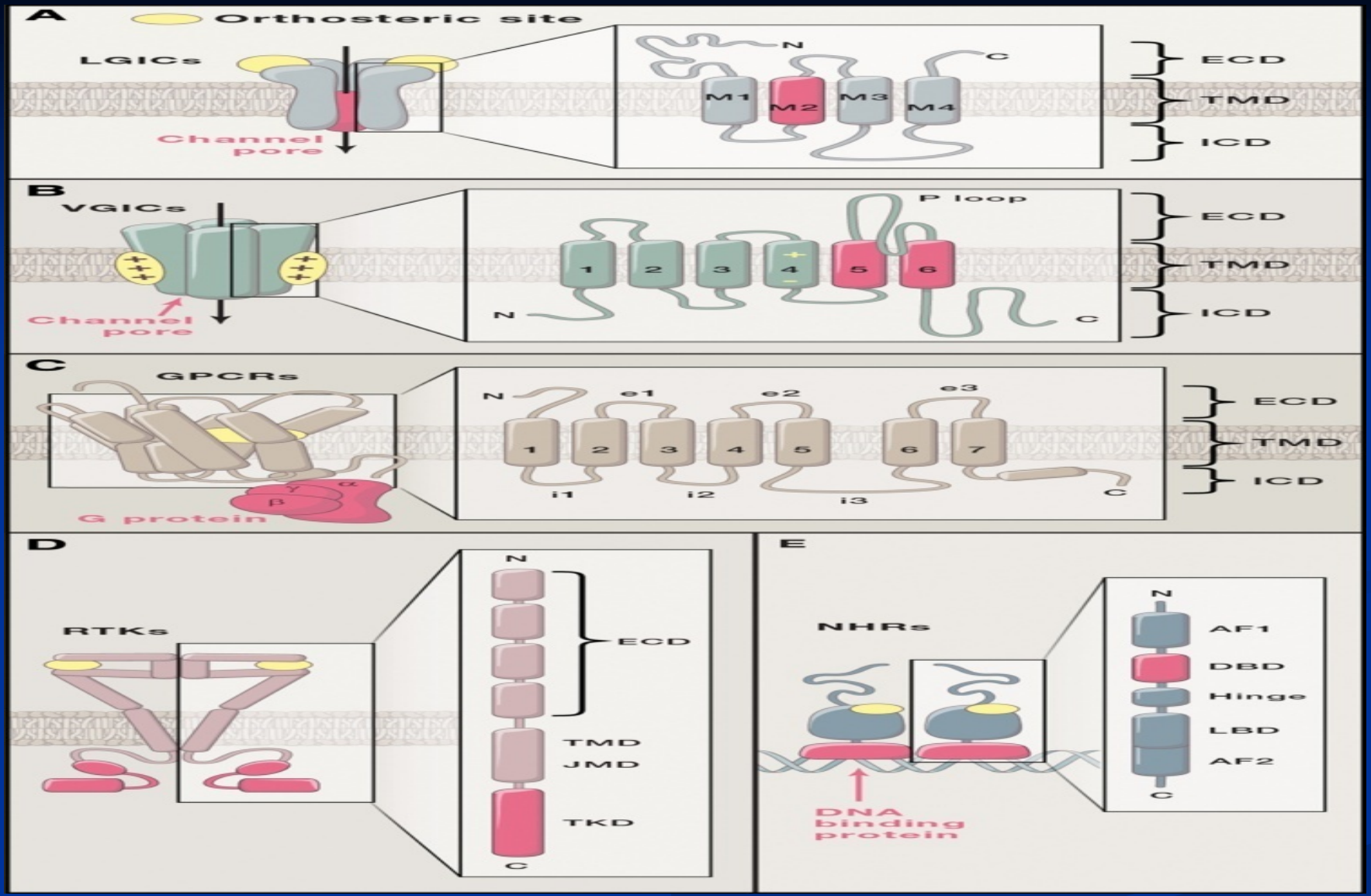


Source: A.J. Trevor, B.G. Katzung, M. Kruidering-Hall: Katzung & Trevor's Pharmacology: Examination & Board Review, 11th Ed.
www.accesspharmacy.com

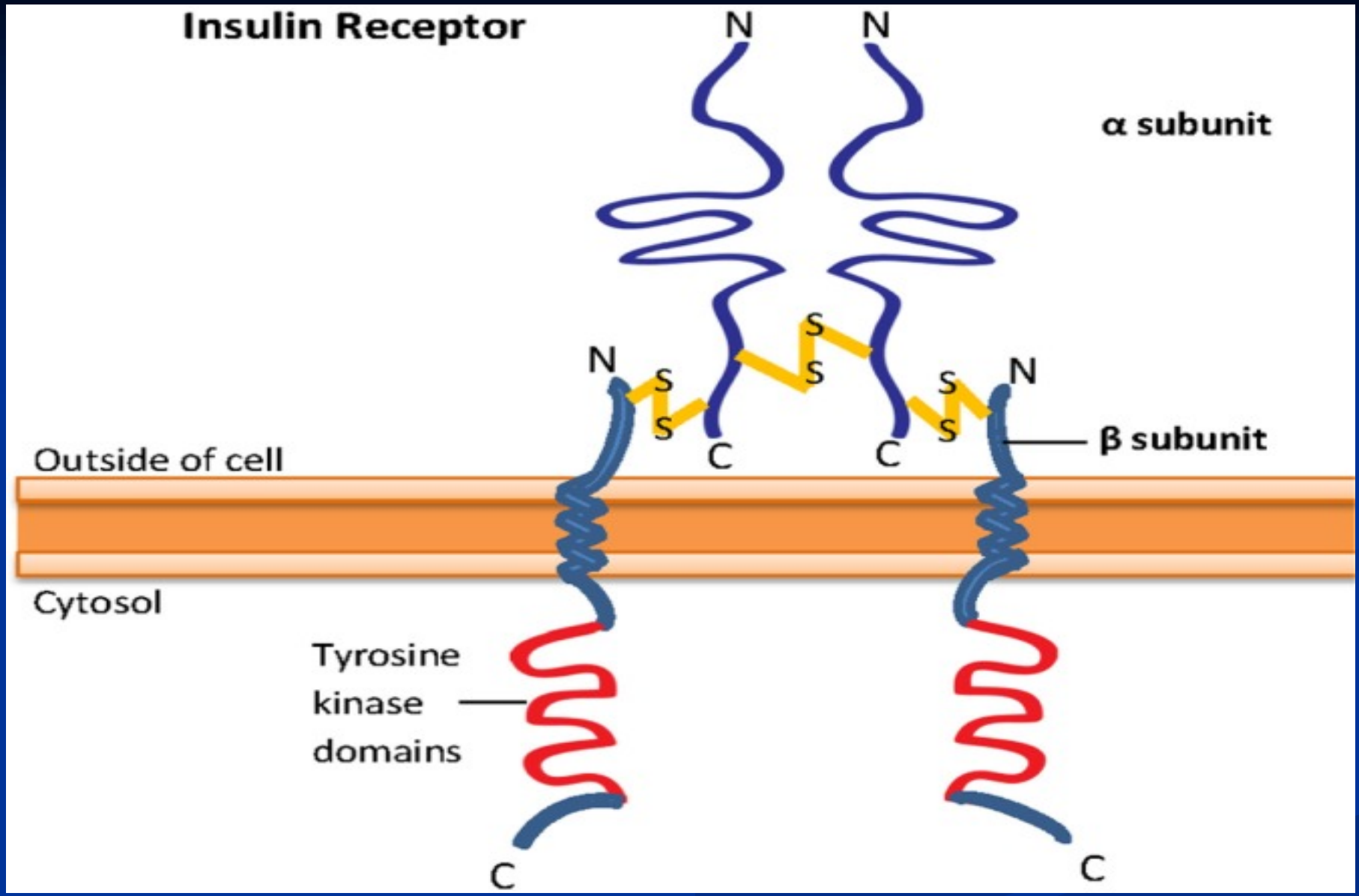


Schematic representation of the major receptor superfamilies

Diabetes Obes Metab. 2017 Sep;19 Suppl 1:4-21. doi: 10.1111/dom.12959.

Allosteric modulation as a unifying mechanism for receptor function and regulation.

Changeux JP, Christopoulos A



β-Adrenergic Receptor and Insulin Resistance in the Heart.

iomol Ther (Seoul). 2017 Jan 1;25(1):44-56. doi: 10.4062/biomolther.2016.128.

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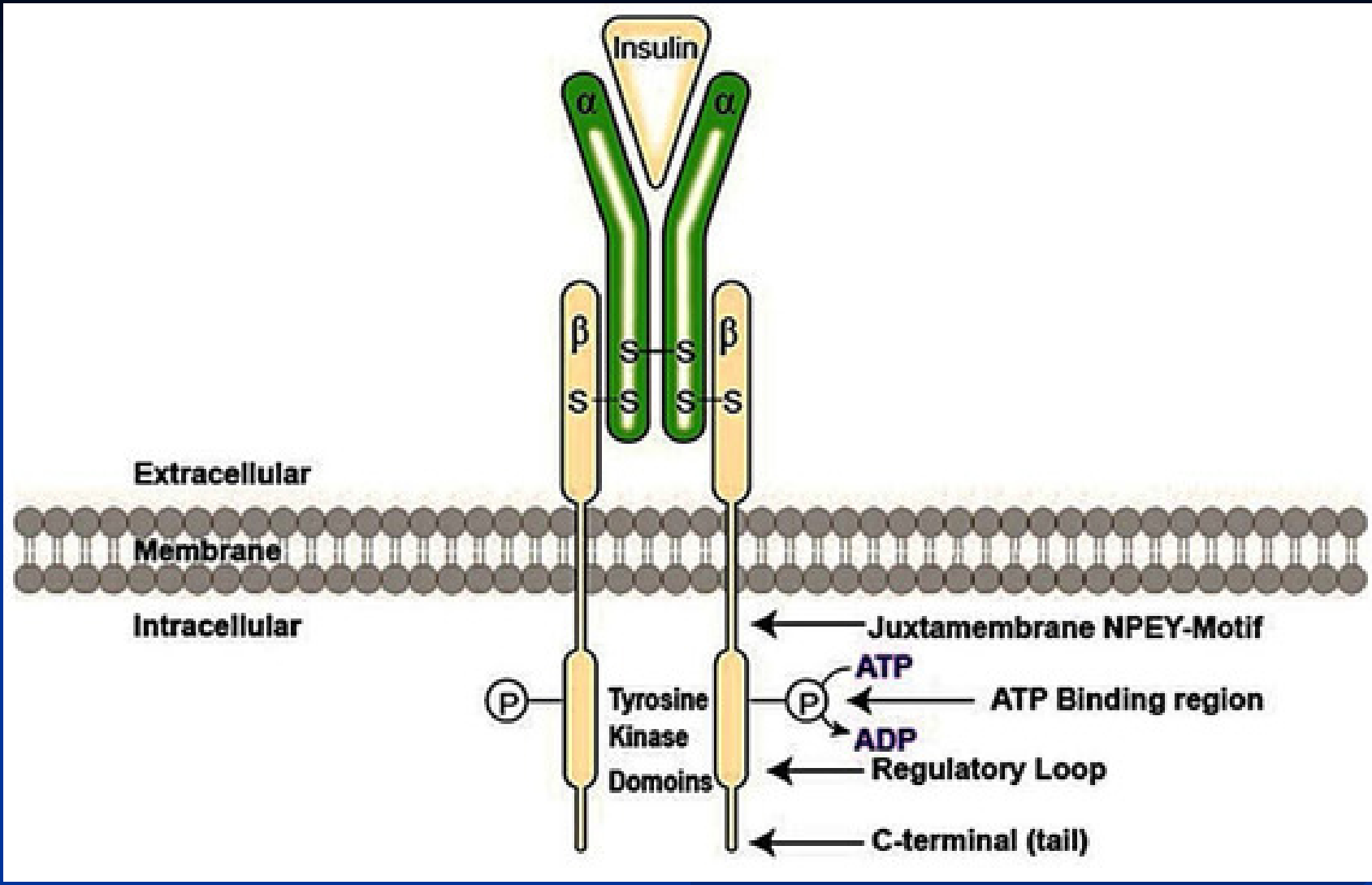
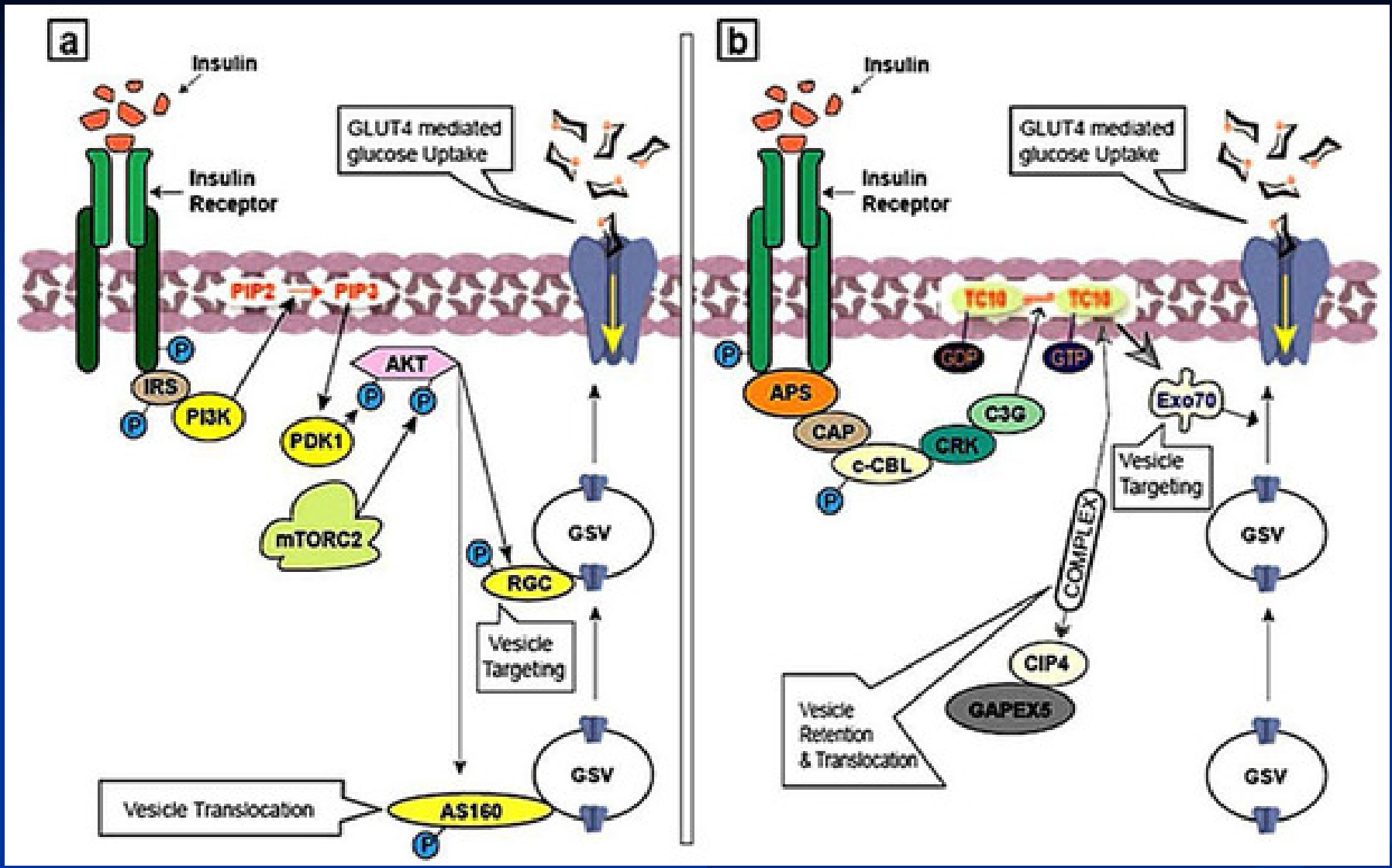


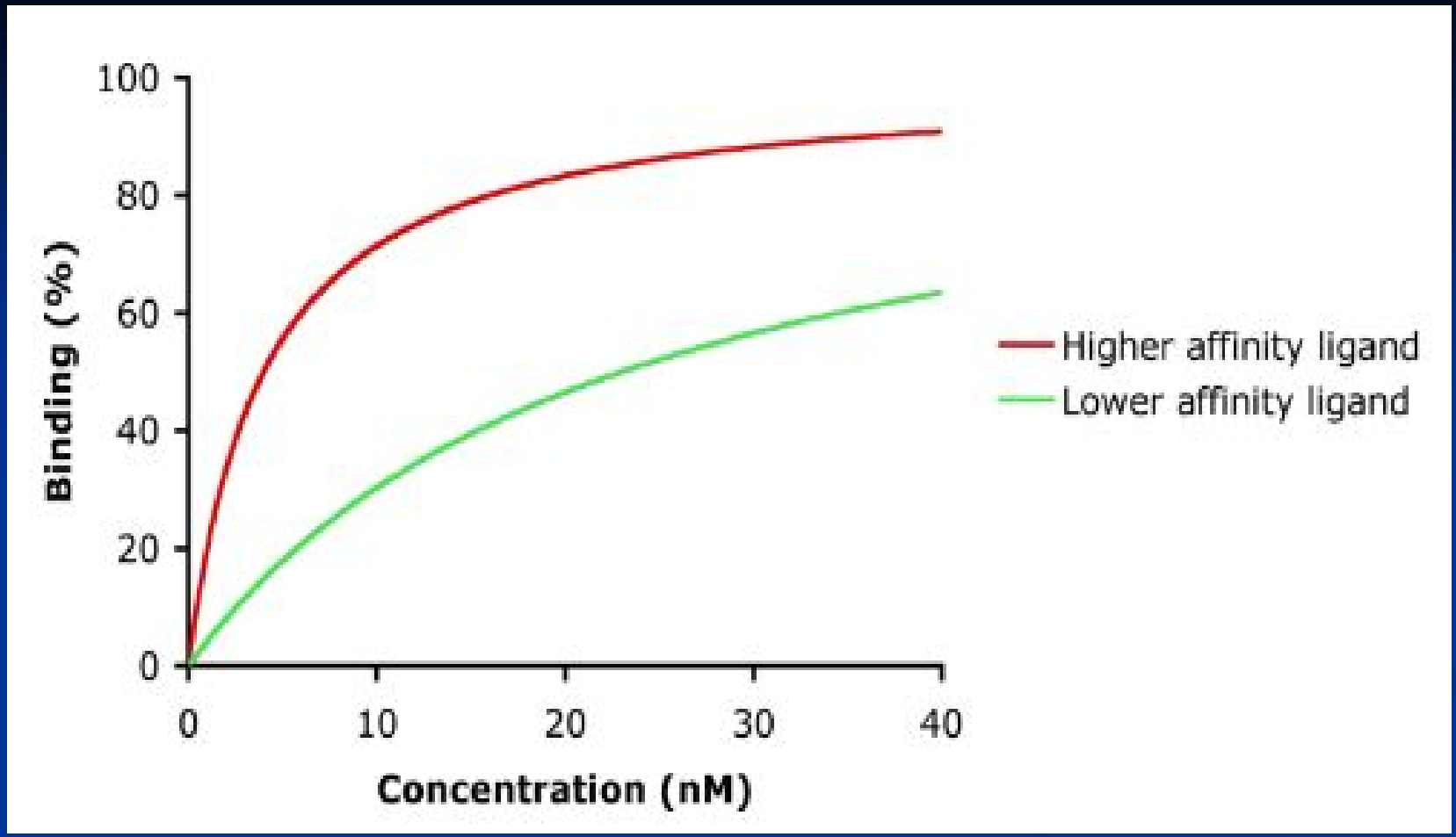
Insulin activates insulin receptor. Subjection of insulin to its receptor brings in the action of insulin and activates insulin receptor which is a type of tyrosine kinase and is comprised of two extracellular α subunits and two cytoplasmic β subunits.

Molecules **2018**, *23*(2), 258; doi:10.3390/molecules23020258 **Sayem et al.**



Insulin signaling cascades regulate GLUT4 trafficking by intracellular itinerary. Visualization of the whole-body glucose homeostasis.

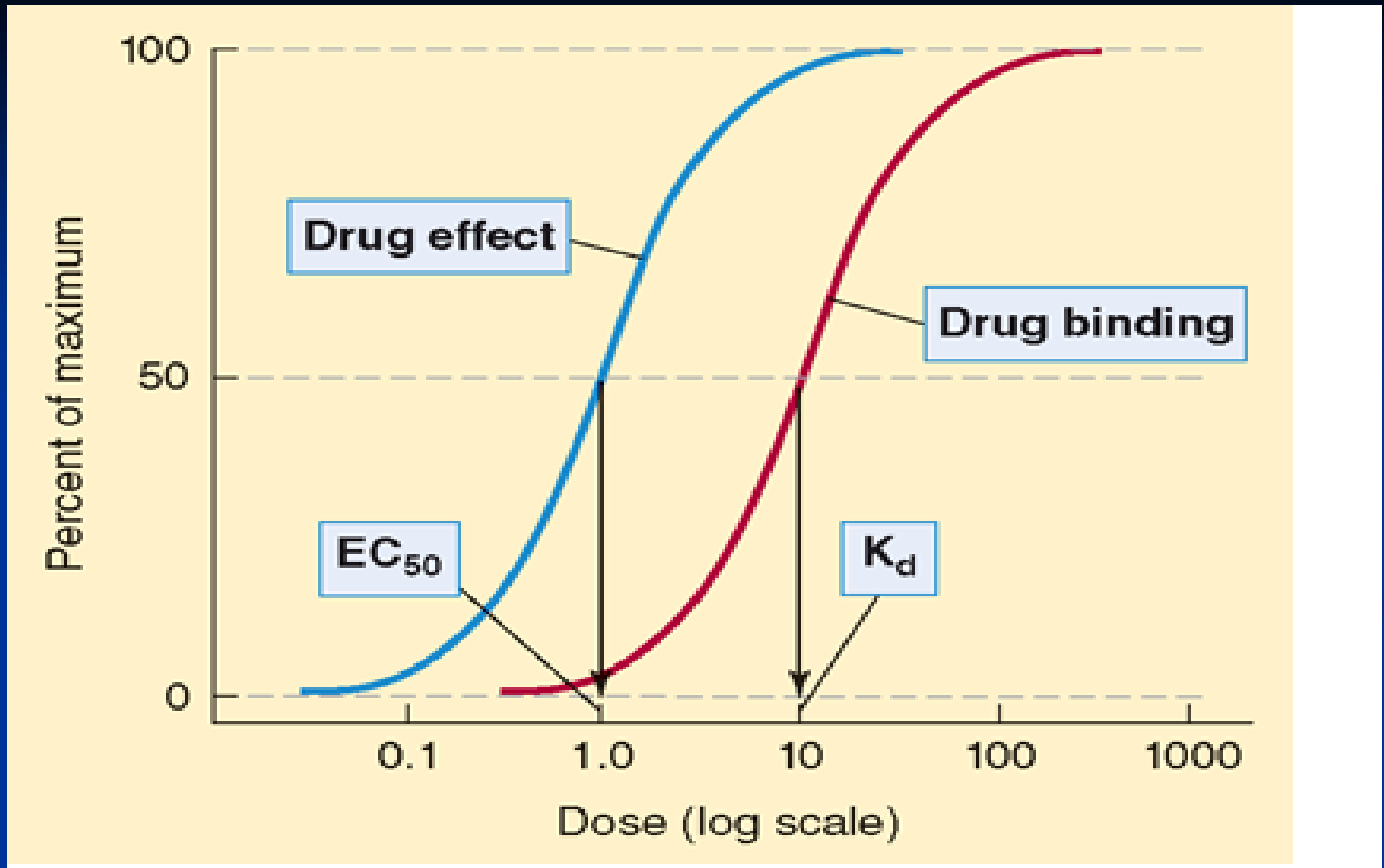
Molecules **2018**, *23*(2), 258; doi:10.3390/molecules23020258 **Sayem et al.**



Affinity

Affinity is the **measure of the strength of the bond between the drug and its receptor**. Affinity of a drug to its receptor helps determine the dose of the drug: low affinity would indicate the need of a higher dose to form enough drug-receptor complexes that would lead to a significant effect .

https://www.lecturio.com/magazine/pharmacodynamics/



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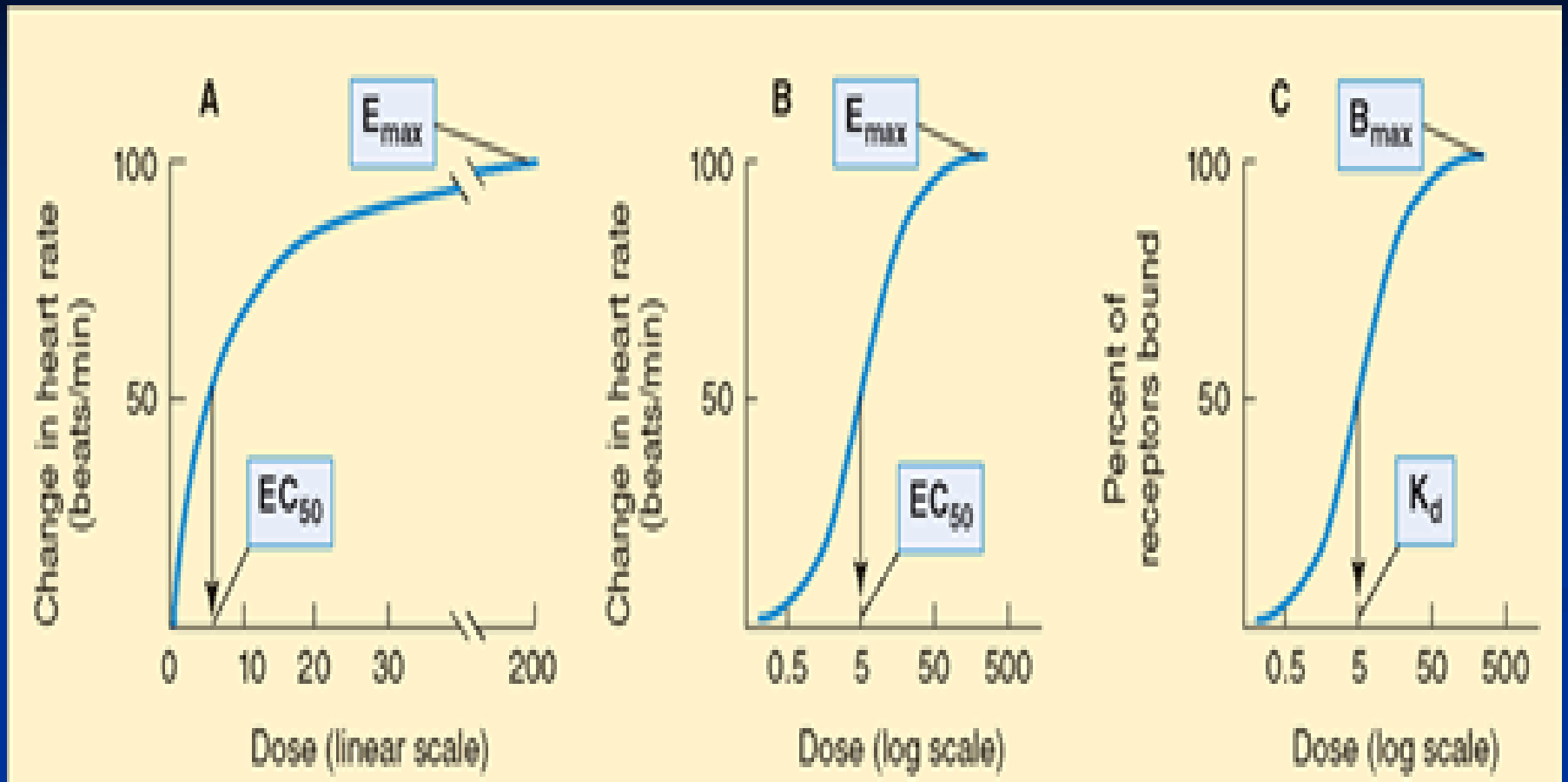

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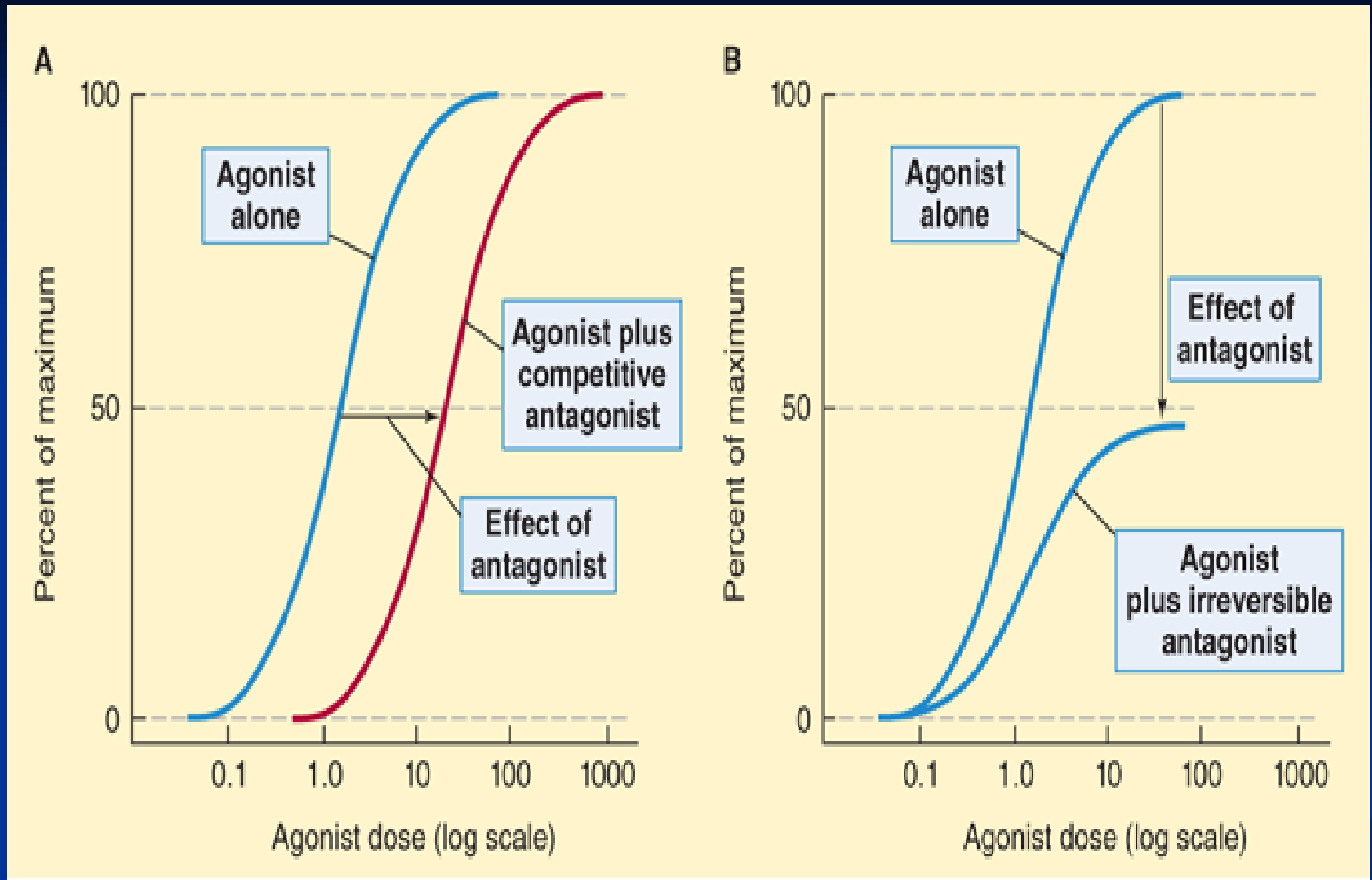

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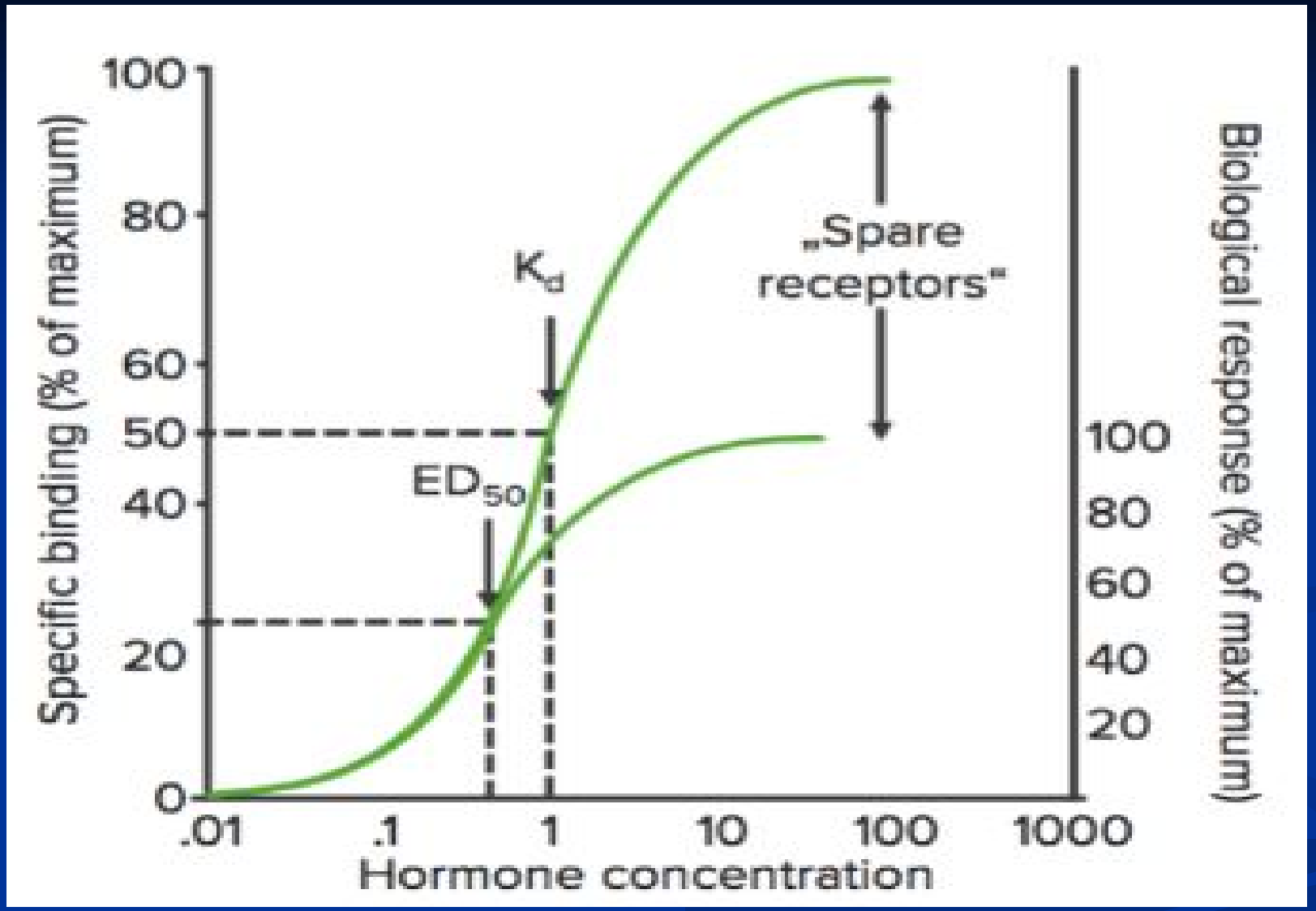

Spare Receptors

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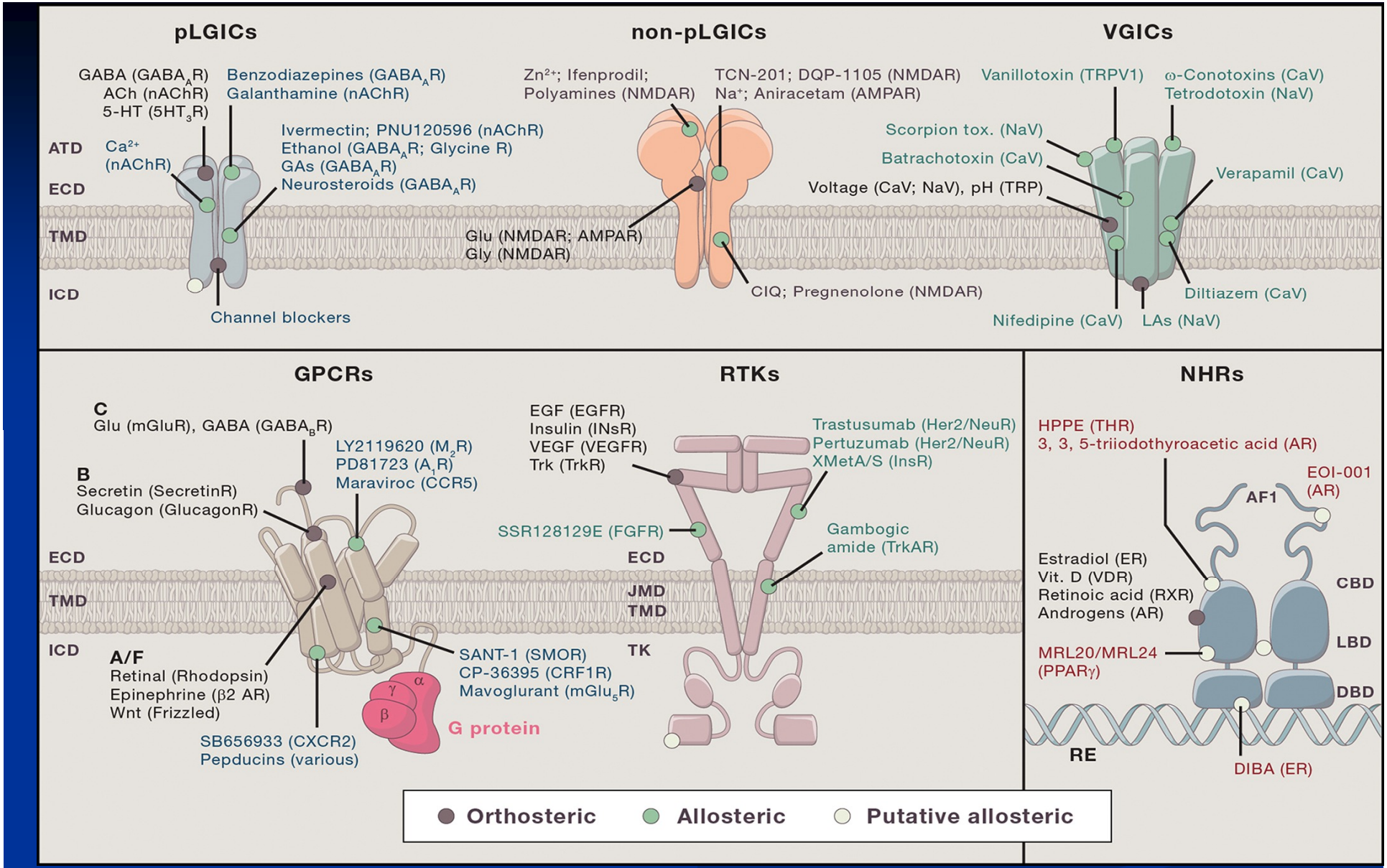
THE PHENOMENON OF "BIASED AGONISM"

The concept of "biased agonism"—i.e., the ability of a ligand to stabilize distinc conformations of a given receptor such that only a subset of the possible signaling pathways mediated by that receptor are engaged, to the relative exclusion of othe pathways—was first explicitly defined in studies of GPCRs. For example, Azzi e al. demonstrated that previously classified "beta-blockers" (i.e., clinically used competitive antagonists of the β_2 adrenergic receptor) could actually *activate* th MAP kinase pathway as agonists in a β-arrestin-dependent bu G-protein-independent manner, thus highlighting the potential for the occurrence o multiple active conformations that differentially recognize transducers. Thi phenomenon was extended to various classes of GPCRs,and biased agonism now represents a major paradigm in GPCR drug discovery.The same phenomenon may exist in even earlier studies of NHRs, specifically in the context of compounds termed "selective NHR modulators," with tamoxifen being a prototypical example a the estrogen receptor. This drug demonstrates either pro-estrogenic o anti-estrogenic actions in a tissue-specific manner, thus being the first example of a "selective estrogen receptor modulator."



A multiplicity of allosteric modulatory sites across all receptor superfamilies.

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