USMLE REVIEW COURSE

PHARM Lecture # Three

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Pharmacodynamics

ZMedicalEducation.com

Pharmacodynamics

- The biochemical and physiologic mechanisms of drug action

What the drug

does when it gets there?.

Drug Mechanisms

- Receptor interactions
- Non-receptor mechanisms

Pharmacodynamics: Mechanisms of Action

- Receptor interaction
- Enzyme interaction
- Nonspecific interactions

Non-receptor Mechanisms

- Actions on Enzymes
  - Enzymes = Biological catalysts
  - Drugs alter processes catalyzed by the enzymes
  - Examples
    - Cholinesterase inhibitors
    - Monoamine oxidase inhibitors

Non-receptor Mechanisms

- Combining With Other Chemicals
  - Antacids
  - Antiseptic effects of alcohol, phenol

  - Chelation of heavy metals

  . Changing Cell Membrane Permeability

Non-receptor Mechanisms

- Anti-metabolites
  - Enter biochemical reactions in place of normal substrate “competitors”
  - Result in biologically inactive product
  - Examples
    - Some anti-neoplastics
    - Some anti-infectives

Agonists and Antagonists

AGONIST

- A drug is said to be an agonist when it binds to a receptor and causes a response or effect.

It has intrinsic activity = 1

Agonists and Antagonists

ANTAGONIST

- A drug is said to be an antagonist when it binds to a receptor and prevents (blocks or inhibits) a natural compound or a drug to have an effect on the receptor. An antagonist has NO activity.

  Its intrinsic activity is = 0

Agonists and Antagonists

PHARMACOLOGICAL ANTAGONISTS

1. Competitive
   They compete for the binding site

   - Reversible
   - Irreversible

2. Non-competitve
   Bind elsewhere in the receptor (Channel Blockers

Agonists and Antagonists

FUNCTIONAL ANTAGONISTS

1. Physiologic Antagonists

2. Chemical Antagonist

Agonists and Antagonists

Physiologic ANTAGONIST

- A drug that binds to a non-related receptor, producing an effect opposite to that produced by the drug of interest.

- Its intrinsic activity is = 1, but on another receptor.

Glucocorticoid Hormones	↑ Blood Sugar
Insulin	↓ Blood Sugar

Agonists and Antagonists

Chemical ANTAGONIST

- A chelator (sequester) of similar agent that interacts directly with the drug being antagonized to remove it or prevent it from binding its receptor.

- A chemical antagonist does not depend on interaction with the agonist's receptor (although such interaction may occur).

Heparin, an anticoagulant, acidic

If there is too much → bleeding and haemorrhaging

Protamine sulfate is a base. It forms a stable inactive complex with heparin and inactivates it.

Agonists and Antagonists

Synergism

The combined effect of two drugs is higher than the sum of their individual effects.

Additivity

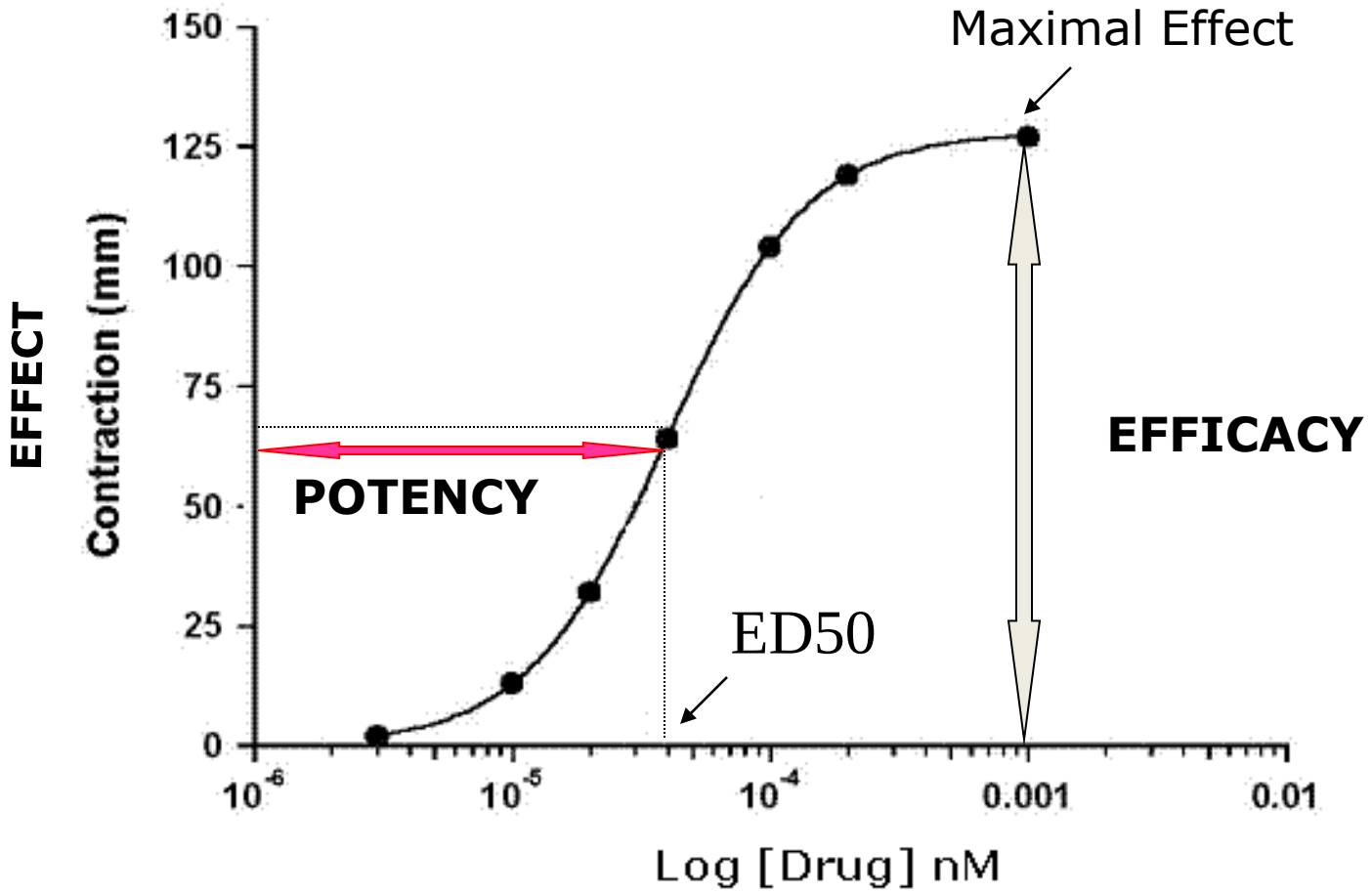
The combined effect of two drugs is equal to the sum of their individual effects.

Agonists and Antagonists

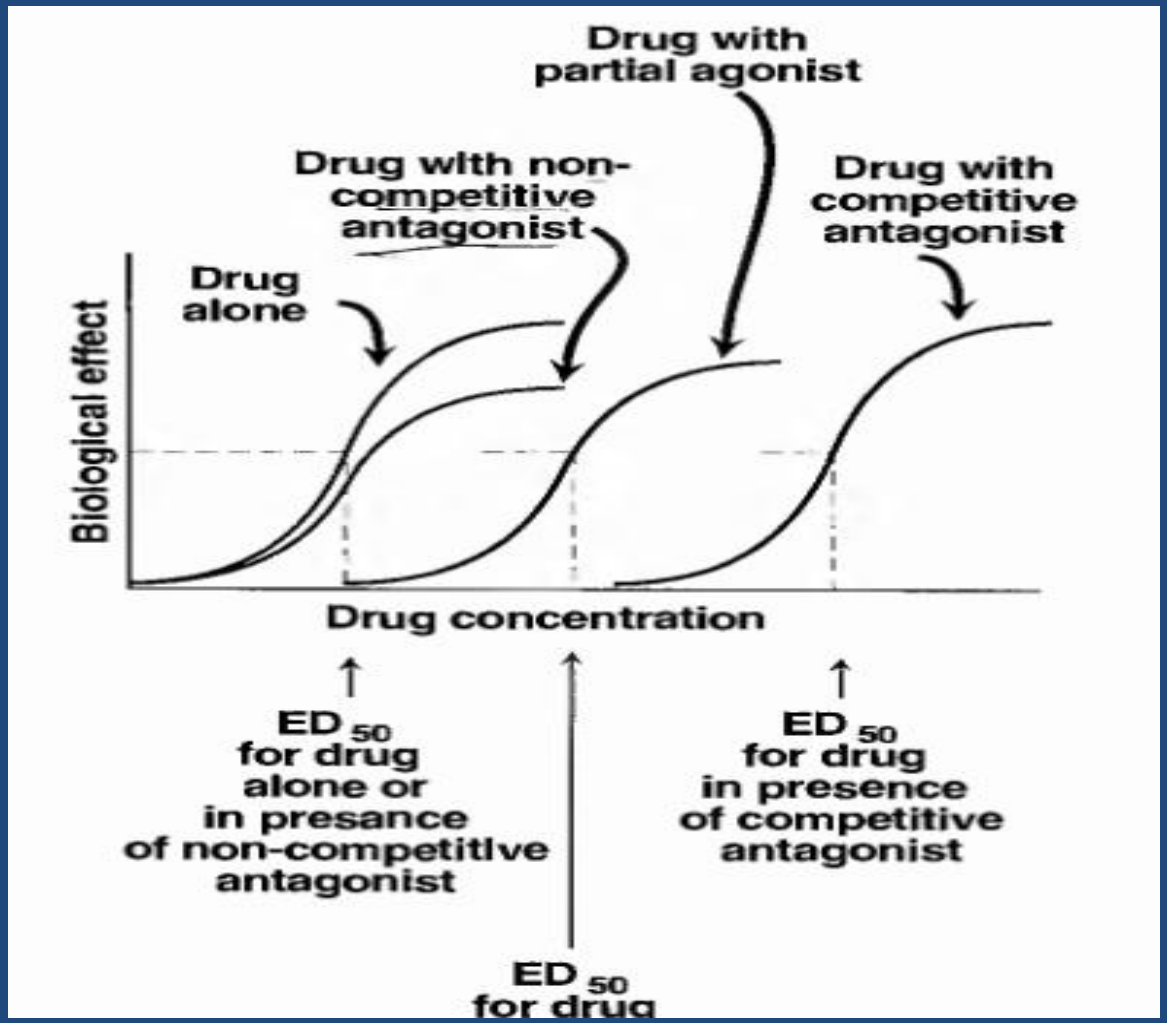
PARTIAL AGONIST

- A drug is said to be a partial agonist when it binds to a receptor and causes a partial response.
- It has intrinsic activity < 1.

SEMILOG DOSE-RESPONSE CURVE



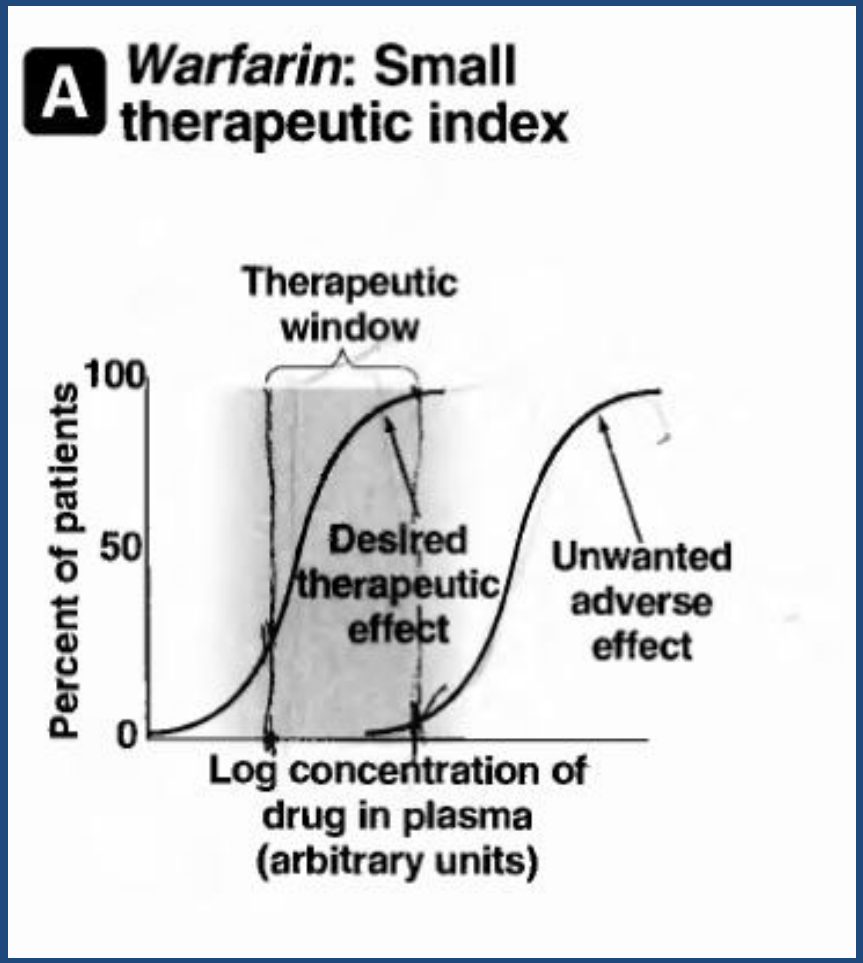
Pharmacodynamics:

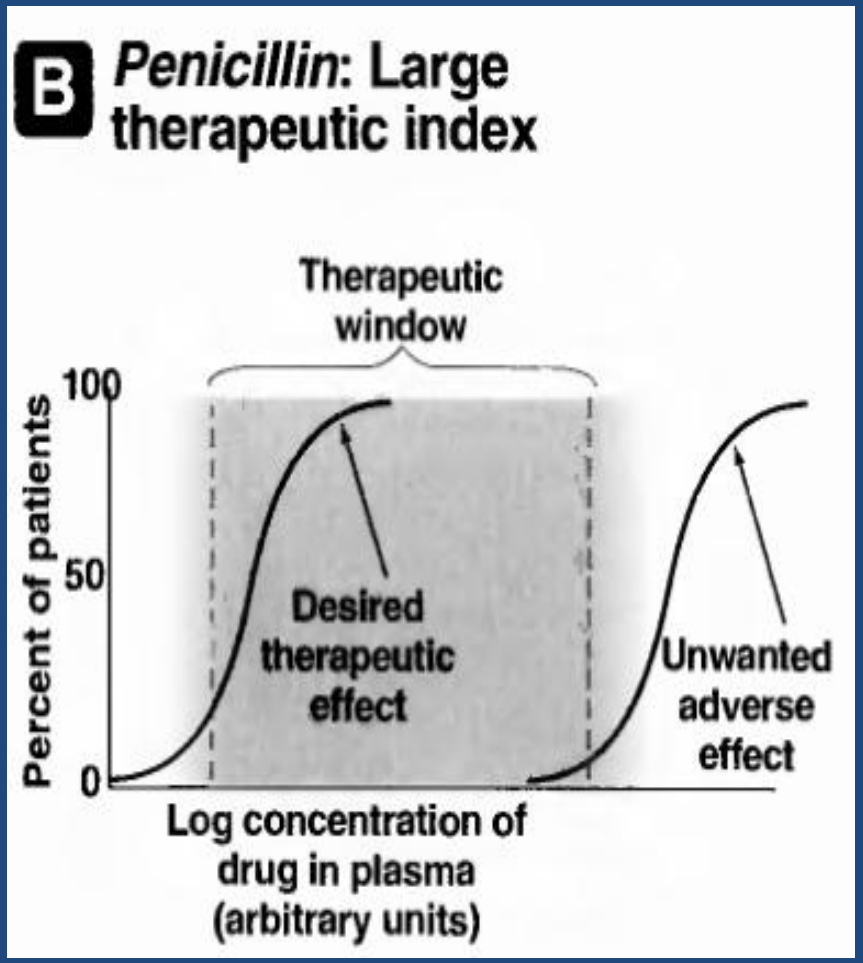


Effects of drug antagonists.

Reproduced from Lippicott's, 2007

Cumulative percent of patients responding to plasma levels of drugs





Reproduced from Lippicott's, 2007

Pharmacotherapeutics: Monitoring

- Therapeutic index
- Drug concentration
- Patient's condition
- Tolerance and dependence
- Interactions
- Side effects/adverse drug effects

Therapeutic index

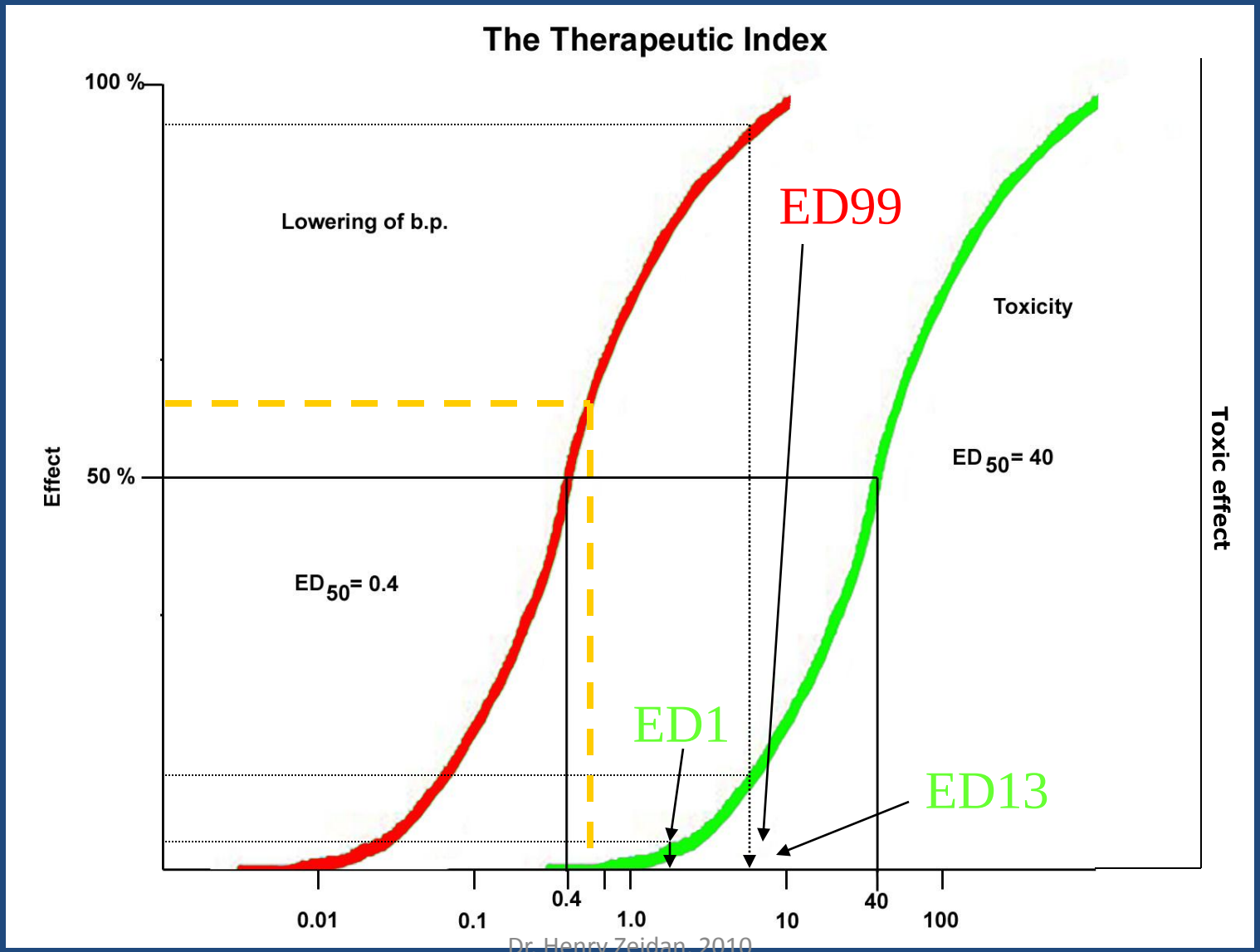
$$\text{Therapeutic Index} = \frac{\text{TxD50}}{\text{ED50}}$$

As long as the slopes of the curves are similar, however, if not similar, we use the Standard Margin of safety:

$$\text{Standard Margin of safety} = \frac{\text{TxD1–1 x 100}}{\text{ED99}}$$

Which determines the percent to which the dose effective in 99% of the population must be raised to cause toxicity in 1% of the population.

Therapeutic Index



Signaling Mechanisms

Dr. Henry Zeidan

Types of Receptors

- **1. Agonist (full or partial) – binds to and activates the receptor**
- **2. Antagonist – binds to the receptor but cause no activation**
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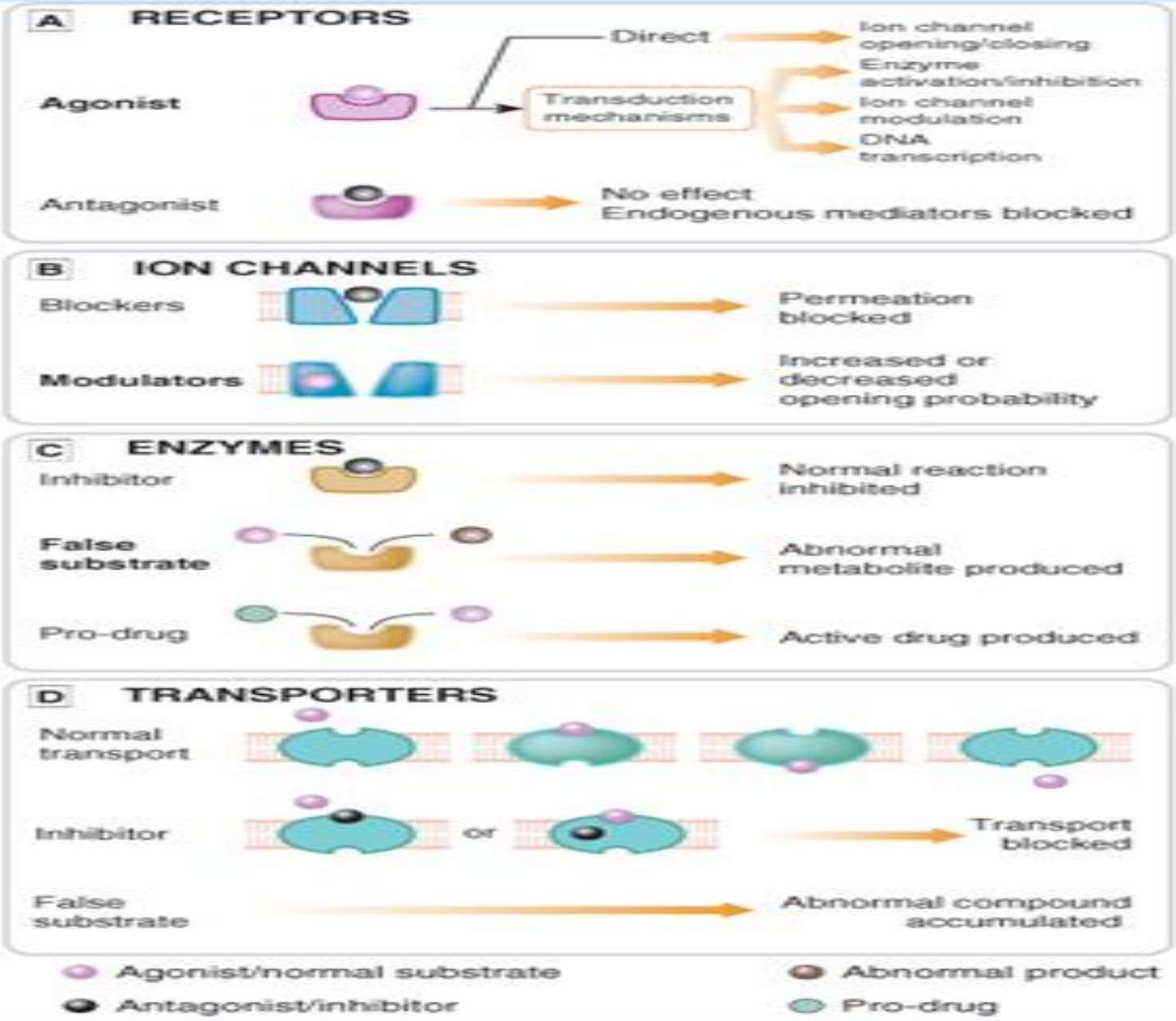
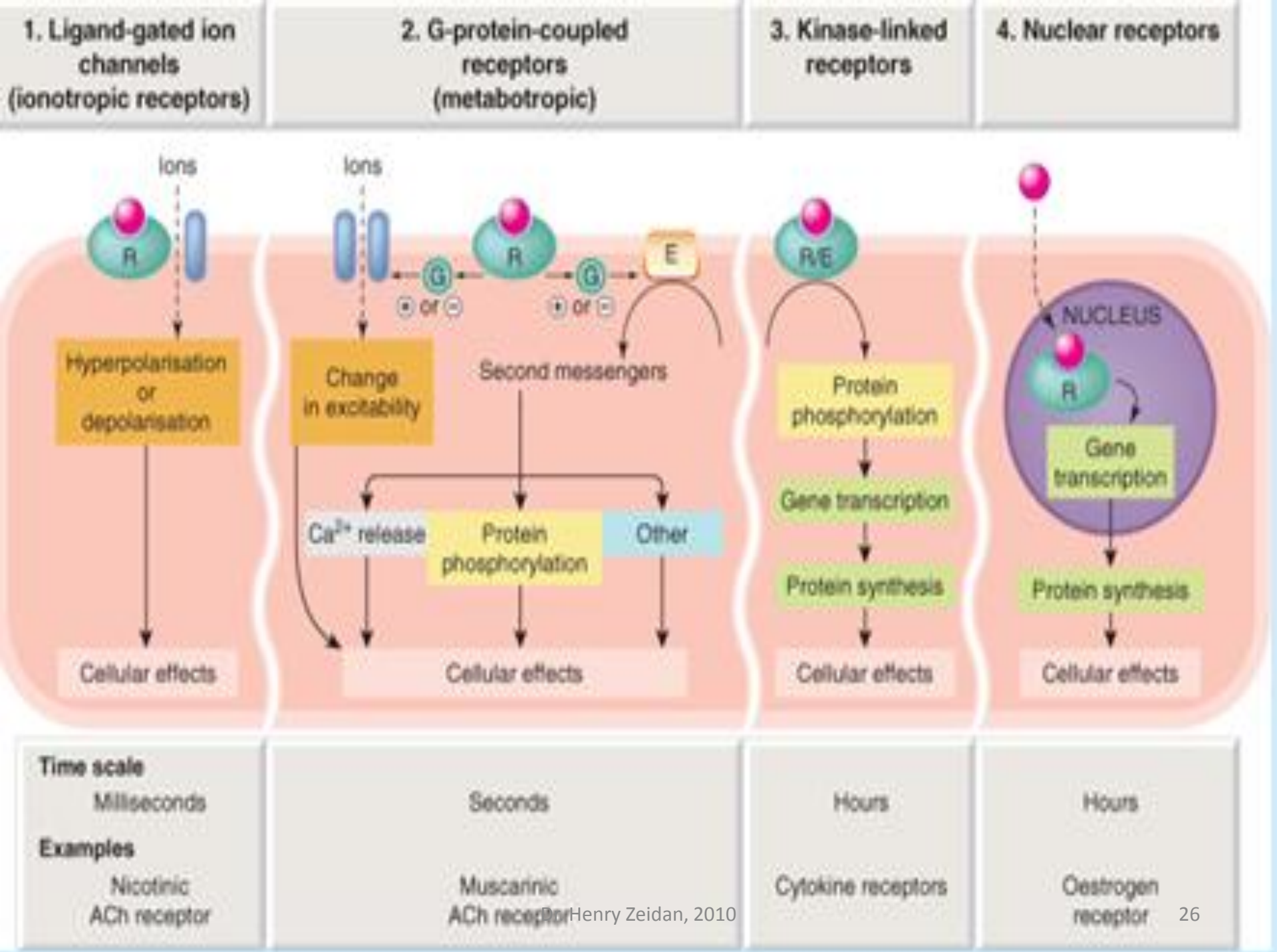
- * A Ligand is a general term for small molecule that binds a receptor.
-



Types of targets for drug action


1. Ligand-gated ion channels (ionotropic receptors)
2. G-protein-coupled receptors (metabotropic)
3. Kinase-linked receptors
4. Nuclear receptors
Ions
R
Hyperpolarisation or depolarisation
Cellular effects
Ions
R
G
or
R
G
or
E
Change in excitability
Second messengers
Ca2+ release
Protein phosphorylation
Other
Cellular effects
R/E
Protein phosphorylation
Gene transcription
Protein synthesis
Cellular effects
NUCLEUS
R
Gene transcription
Protein synthesis
Cellular effects
Time scale
Milliseconds
Seconds
Hours
Hours
Examples
Nicotinic ACh receptor
Muscarinic ACh receptor
Cytokine receptors
Oestrogen receptor

Intracellular Receptors

- Binding of hormones or drugs releases regulatory proteins permitting dimerization of the hormone-receptor complex. These complexes in turn Interact with key response elements on nuclear DNA to modify gene expression and changing protein synthesis.

Intracellular Receptors(Cont'd)

- Include receptors of adrenal & gonadal steroids, thyroid hormones and vitamin D

Membrane Receptors Directly Coupled To Ion Channels

A) Nicotinic receptors for Ach which is coupled to a Na^+/K^+ ion channel.

A) $GABA_A$ receptors in CNS, coupled to chloride channel

B) Glycine receptors & serotonin receptor subtype.

C) Response is rapid

Ion Channel-linked receptors(Cont'd)

Ligands that "gate" the channels are neurotransmitters

Examples of Specific receptors of the "Nicotinoid" type

1) Nicotinic acetylcholine receptors

2) $GABA_A$ **($GABA_A$ receptors bind to benzodiaepines such as diazepam (Valium))** receptors are Cl^- channels

3) $GABA_C$ – also a Cl^- channels

4) Glycine -- Cl^- channel which is blocked by strychnine

Ion Channel-linked receptors

- Ion channels are responsible for the conductance of ions
- such as sodium, potassium, calcium, and chloride
- across membranes. The action of these channels will affe
- the polarization states of the cell membrane.
- Ion channels act as
- the molecular mediators of the polarization state of the cell.

Numerous drugs are targeted to these channels (which makes them receptors too, in a sense) and have a significant impact on a diverse number of disease states

G-Protein Coupled Receptors
What are they?

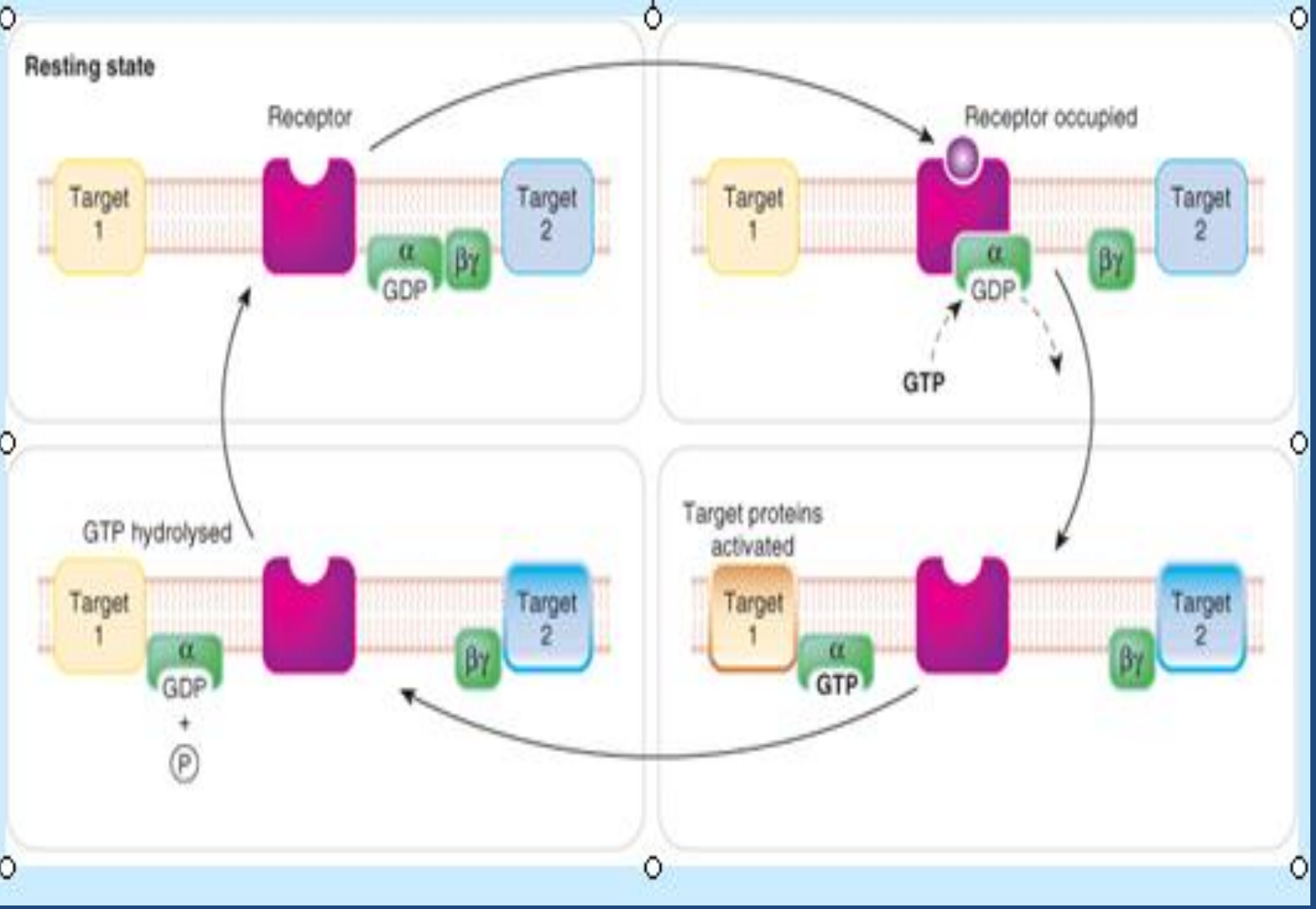
- 7 transmembrane (membrane spanning) a-helices form a bundle which is the site of ligand binding . The intracellular loops couple primarily with G-proteins and other effectors.
-

Receptors Coupled with G-Proteins

- Receptors coupled to adenylyl cyclase via G-proteins.

  Adenylyl cyclase in turn forms cAMP as a specific mediator to activates protein kinase A, which in turn Phosphorylates tissue specific enzymes.

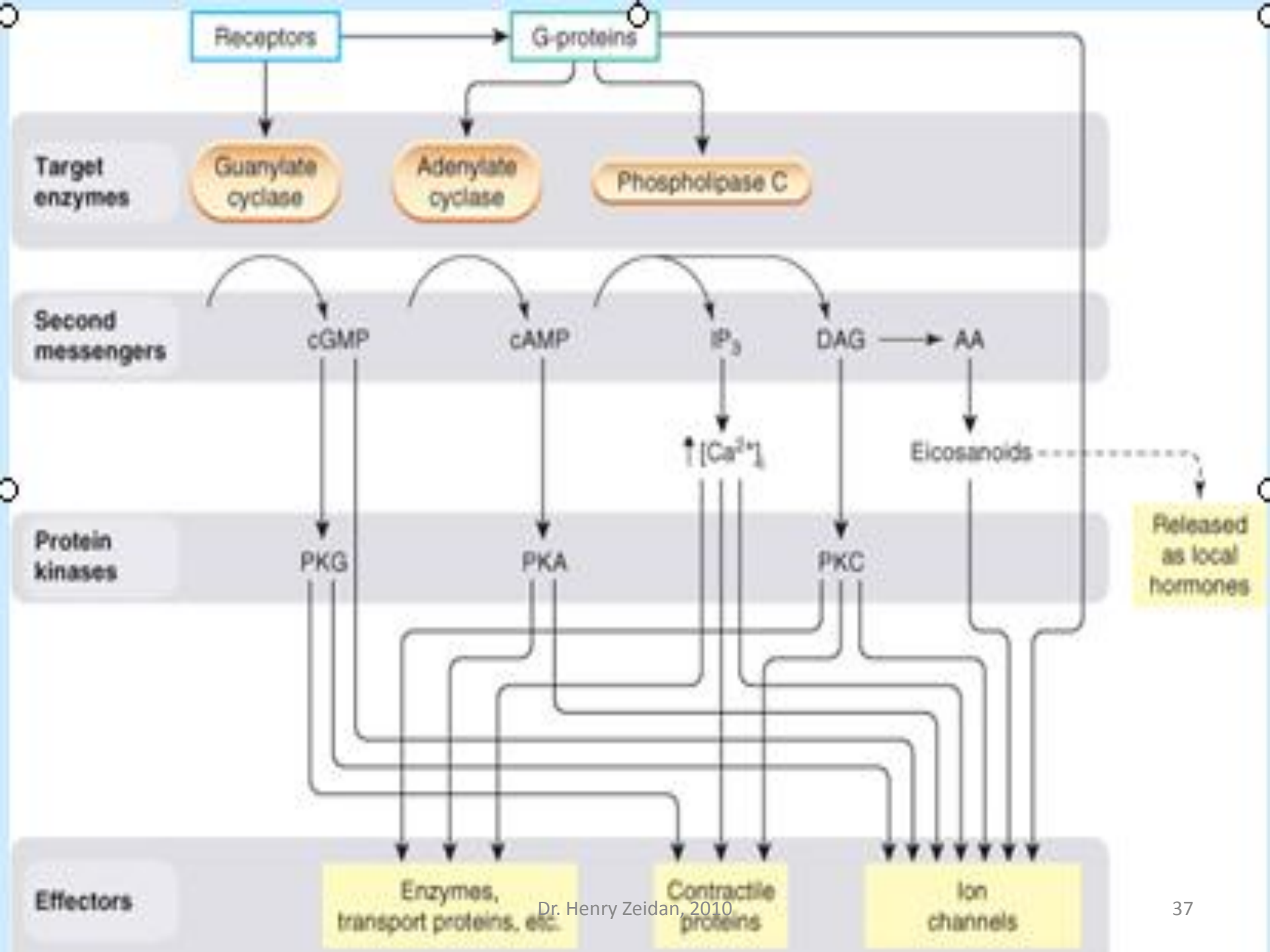
- Receptors linked to Gs proteins increasing cAMP include catecholamines(alpha2), Dopamin(D1), glucagon, histamine (H2) and 5 HT.



The function of the G-protein

Receptors Coupled with G-Proteins(Cont'd)

- Receptors linked to Gi proteins decreasing cAMP include those for catecholamine (alpha2), Ach muscarinc (M2),Dopamine (D2) and several opiod & 5HT subtypes.


Receptors
G-proteins
Target enzymes
Guanylate cyclase
Adenylate cyclase
Phospholipase C
Second messengers
cGMP
cAMP
IP_3
DAG
AA
$\uparrow[Ca^{2+}]_i$
Eicosanoids
Protein kinases
PKG
PKA
PKC
Released as local hormones
Effectors
Enzymes, transport proteins, etc.
Contractile proteins
Ion channels

Receptors Linked via G-proteins to Phospholipase C

- Receptor systems are coupled to Gα proteins which activates phospholipase C to release Inositol triphosphate (IP3) & diacylglycerol (DAG) from membrane PIP3. IP3 releases Ca++ from SR which DAG activates protein kinase C resulting in Phosphorylation of tissue specific enzymes.

Receptors Linked via G-proteins to Phospholipase C(Cont'd)

- Examples for these receptors are Ach (M1 & M3), norepinephrine (alpha 1), angiotensin II and several opoid & 5HT subtypes

cGMP & Nitric Acid Signaling

- Very important regarding vascular smooth muscle
- cGMP is a 2nd messenger in vasculature, facilitating
- dephosphorylation of myosin light chains preventing

  their interaction with actin-thus causing vasodilation.
- Nitric oxide (NO), which can be formed from nitrates

cGMP & Nitric Acid Signaling

- Nitric oxide (NO), which can be formed from nitrates (e.g. nitroglycerin) and released from endothelial cells by vasodilators (eg, H1 & H2 agonists) activates guanylyl cyclase increasing cGMP.

Receptors that function as Enzymes or Transporters

- Enzyme inhibitors include those for the following enzymes;

- Carbonic anhydrase, cyclooxygenase, dihydrofloate reductase, DNA/RNA plotmerases, monoamine oxidases, Na+-K+ ATP-ase, reverse transcriptase.

- Drugs that inhibit transporter systems include those for transporters involved in reuptake of dopamine, GABA, norepinephrine & 5HT.

Receptors That Function as Transmembrane Enzymes

- Mediate first steps in signaling by insulin and growth factors including Endothelial Growth factor (EGF), Platelet Derived Growth Factor (PDGF)

- Membrane- spanning macromolecules with recognition sites for binding of insulin & growth factors located extracellulally and domains that function as tyrosine kinases.

Receptors That Function as Transmembrane Enzymes(Cont'd)

- Binding of a ligand causes conformational changes so that the tyrosine kinase domains are activated leading to phosphorylation of tissue specific proteins

Receptors for Cytokines

- Include receptors for somatotropin & interferons
- Are membrane –spanning and activate seprate tyrosine kinases,

  Which in turn Phosphorylates signal transducers & activators

  that modify gene transcription

GPCRs and Cell signalling

Example: β-adrenergic receptors stimuate G_s type G-proteins ('s' stands for stimulatory) which, in turn, activates adenylate cylase to make cyclic AMP (cAMP) while α-adrenergic receptors stimuate G_i type G-proteins ('i' stands for inhibitory) which, in turn, inhibits adenylate cylase and reduces the amount of cAMP.

Adrenergic receptors

- Norepinephrine (noradrenaline) and epinephrine (adrenaline) are catecholamine neurotransmitters. They are the most important neurotransmitter of the sympathetic branch of the autonomic nervous system. The receptors for adrenaline are good examples of and were among the first GPCRs.

Muscarinic receptors

-sensitive to muscarine of poisonous mushrooms

►5 subtypes

-M_1, M_2, M_3, M_4, M_5

-are all GPCRs

-M_1, M_3, M_5- coupled to G_q type G-proteins→ activates PLC

-M_2, M_4,-coupled to G_i-type G-proteins → inhibits adenylate cyclase)

Neurotransmitter transporters

Epinephrine, dopamine, serotonin acetylcholine and monoamines, all have a specific transporter . They al are Na+/K+ co-transporters. Prozac, the well-known antidepressent, interacts with and inhibits the serotonin transporter (Prozac belong to a class of drugs known as SSRIs – *selective* serotonin reuptake inhibitors). Cocaine is known to bind several neurotransmitter transporters (most notably the dopamine transporter).

References:

- 1. Betram G. Katzung, Basic & Clinical Pharmacology, Ninth Edition, McGraw Hill

  Richard A. Harvey, Pamela C. Champe,
- Lippincott's Illustrated Reviews of Pharmacology, 4 edition,

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- Kaplan notes, 2012

WEB Sites

- Howard University
- Howard University Site.htm

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