Pharmacodynamics

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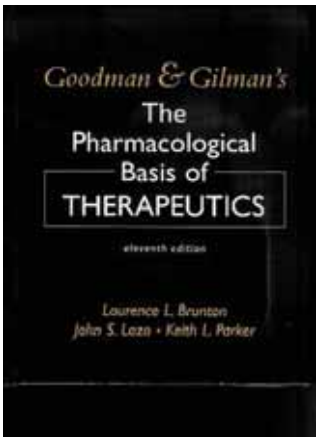
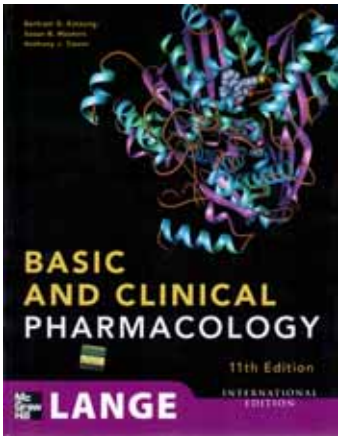
English Pharmacology Textbooks





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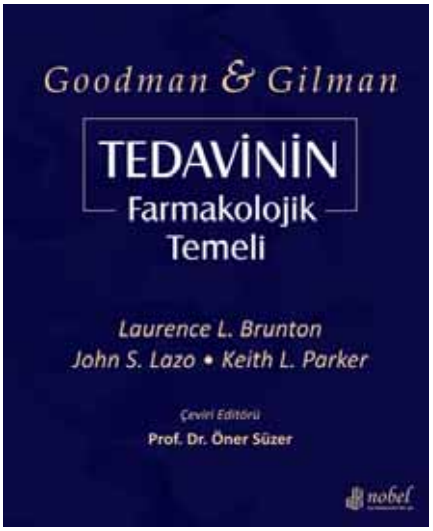

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Contents of the lecture

- **Pharmacodynamics deals with what drugs do for human body.**
- **Subjects to be discussed:**
  - **Mechanisms of drug actions**
  - **Drug-receptor interaction**
  - **Dose (concentration) - effect relationship**
  - **Factors that modify drug actions and drug interactions**
  - **Adverse drug reactions (drug toxicology)**

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Molecular targets for drugs I

- **Enzymes such as:**
  Acetylcholine esterase, choline acetyltransferase, cyclooxygenase, xanthine oxidase, angiotensin-converting enzyme, carbonic anhydrase, HMG-CoA reductase, Dopa decarboxylase, monoamine oxidase, dihydrofolate reductase, DNA polymerase…

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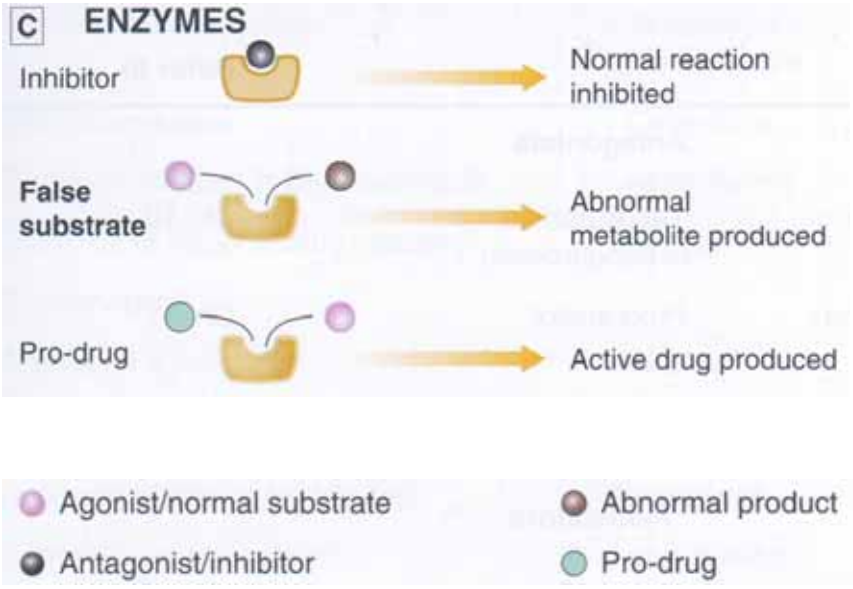

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Enzymes	Inhibitors	False substrates
Acetylcholinesterase	Neostigmine Organophosphates	
Choline acetyltransferase		Hemicholinium
Cyclooxygenase	Aspirin	
Xanthine oxidase	Allopurinol	
Angiotensin-converting enzyme	Captopril	
Carbonic anhydrase	Acetazolamide	
HMG-CoA reductase	Simvastatin	
Dopa decarboxylase	Carbidopa	Methyldopa
Monoamine oxidase-A	Iproniazid	
Monoamine oxidase-B	Selegiline	MPTP
Dihydrofolate reductase	Trimethoprim Methotrexate	
DNA polymerase	Cytarabine	Cytarabine
Enzymes involved in DNA synthesis	Azathiaprine	
Enzymes of blood clotting cascade	Heparin	
Plasminogen*		
Thymidine kinase	Aciclovir	
HIV protease	Saquinavir	
Reverse transcriptase	Didanosine, zidovudine	

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Molecular targets for drugs II

- **Transport proteins such as:**
  Choline transporter at terminal neuron, vesicular norepinefrine uptake, norepinefrine reuptake$_1$, proximal tubular secretion (for weak acids), $Na^+/K^+/2Cl^-$ cotransport at loop of Henle, Na^+/K^+-ATPase pump, proton pump at gastric mucosa...

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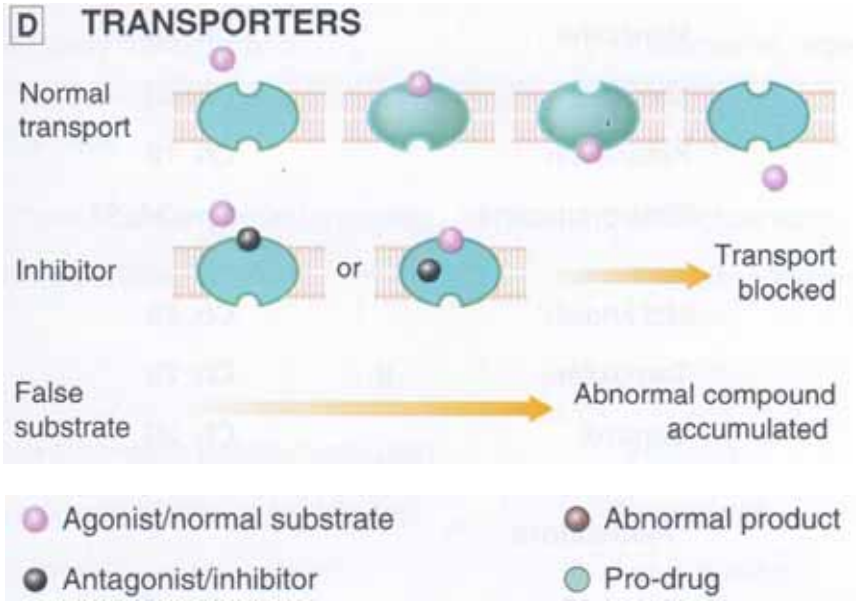

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Carriers	Inhibitors	False substrates
Choline carrier (nerve terminal)	Hemicholinium	
Noradrenaline uptake 1	Tricyclic antidepressants Cocaine	
		Amphetamine Methyldopa
Noradrenaline uptake (vesicular)	Reserpine	
Weak acid carrier (renal tubule)	Probenecid	
$Na^+/K^+/Cl^-$ co-transporter (loop of Henle)	Loop diuretics	
Na^+/K^+ pump	Cardiac glycosides	
Proton pump (gastric mucosa)	Omeprazole	

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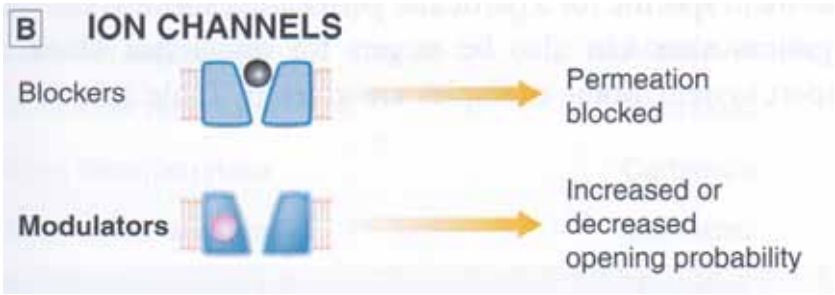
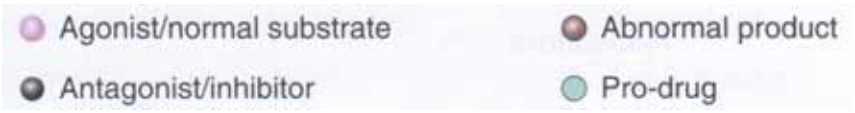
Molecular targets for drugs III

- **Ion channels such as:**
  Receptor or voltage gated Na^+, K^+, Ca^{2+}, Cl^- channels.





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Ion channels	Blockers	Modulators
Voltage-gated sodium channels	Local anaesthetics Tetrodotoxin	Veratridine
Renal tubule sodium channels	Amiloride	Aldosterone
Voltage-gated calcium channels	Divalent cations (e.g. Cd^{2+})	Dihydropyridines Beta-adrenoceptor agonists
Voltage-gated potassium channels	4-Aminopyridine	Many neuromodulators
ATP-sensitive potassium channels	ATP	Cromokalim Sulphonylureas
GABA-gated chloride channels	Picrotoxin	Benzodiazepines
Glutamate-gated (NMDA) cation channels	Dizocilpine, Mg^{2+} Ketamine	Glycine

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Molecular targets for drugs IV

- **Receptors such as:**
  Acetylcholine receptors, adrenergic receptors, histamine receptors, opioid receptors, serotonine receptors, dopamin receptors, prokineticin receptors, insulin receptors, estrogen receptors, progesterone receptors, ryanodine receptors…

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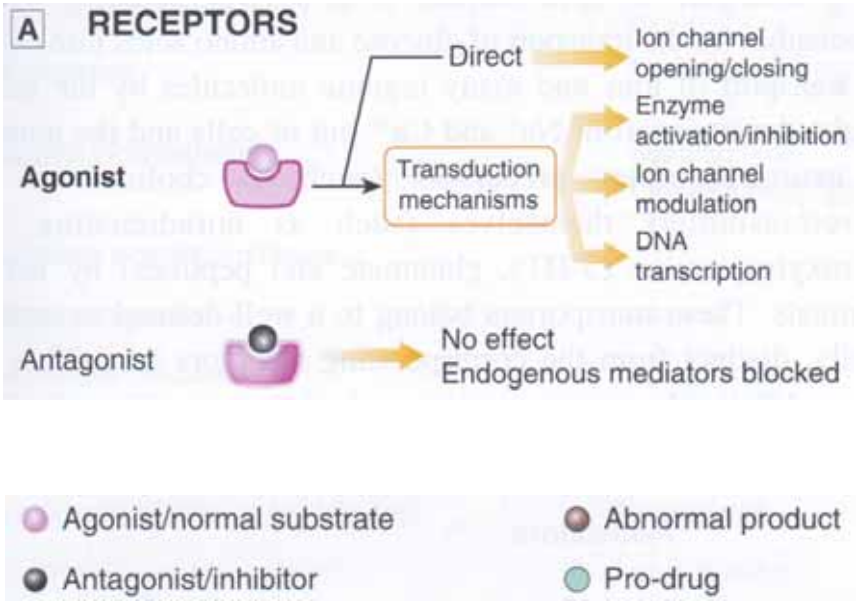

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Receptors	Agonists	Antagonists
Nicotinic ACh receptor	Acetylcholine Nicotine	Tubocurarine α-Bungarotoxin
Beta-adrenoceptor	Noradrenaline (norepinephrine) Isoprenaline	Propranolol
Histamine (H_1-receptor)	Histamine	Mepyramine
Histamine (H_2-receptor)	Impromidine	Ranitidine
Opiate (μ-receptor)	Morphine	Naloxone
5-HT_2-receptor	5-Hydroxytryptamine	Ketanserin
Dopamine (D_2 receptor)	Dopamine Bromocriptine	Chlorpromazine
Insulin receptor	Insulin	Not known
Oestrogen receptor	Ethinylestradiol	Tamoxifen
Progesterone receptor	Norethisterone	Danazol

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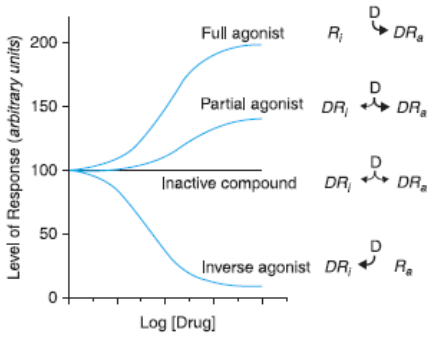
Receptors

- The effects of most drugs result from their interaction with macromolecular components of the organism. These interactions alter the function of the pertinent component and thereby initiate the biochemical and physiological changes that are characteristic of the response to the drug.
- The term ***receptor*** denotes the component of the organism with which the chemical agent is presumed to interact.
- For recent and updated information please refer http://iuphar-db.org

- The concept of drugs acting on receptors generally is credited to John Langley (1878). While studying the antagonistic effects of *atropine* against *pilocarpine* - induced salivation, Langley observed, "There is some substance or substances in the nerve ending or gland cell with which both atropine and pilocarpine are capable of forming compounds." He later referred to this factor as a "receptive substance." The word *receptor* was introduced in 1909 by Paul Ehrlich. Ehrlich postulated that a drug could have a therapeutic effect only if it has the "right sort of affinity." Ehrlich defined a receptor in functional terms: "… that combining group of the protoplasmic molecule to which the introduced group is anchored will hereafter be termed *receptor.*"

Drug-Receptor Binding and Agonism I

- A receptor can exist in at least two conformational states, active (R_a), and inactive (R_i). If these states are in equilibrium and the inactive state predominates in the absence of drug, then the basal signal output will be low.
- The *extent* to which the equilibrium is shifted toward the active state is determined by the *relative affinity* of the drug for the two conformations.



Drug-Receptor Binding and Agonism II

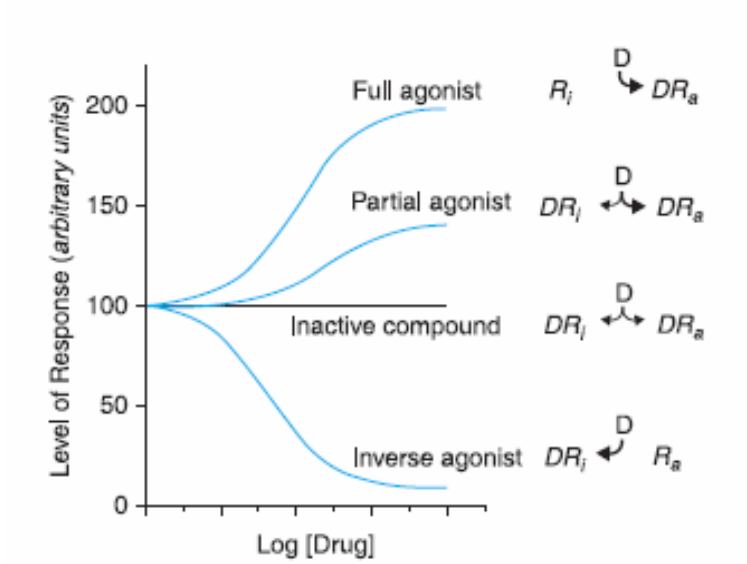
- A drug that has a higher affinity for the active conformation than for the inactive conformation will drive the equilibrium to the active state and thereby activate the receptor. Such a drug will be an agonist.
- A full agonist is sufficiently selective for the active conformation that at a saturating concentration it will drive the receptor essentially completely to the active state.

Drug-Receptor Binding and Agonism III

- If a different but perhaps structurally similar compound binds to the same site on *R* but with only moderately greater affinity for R_a than for R_i , its effect will be less, even at saturating concentrations.
- A drug that displays such intermediate effectiveness is referred to as a ***partial agonist*** because it cannot promote a full biological response at any concentration.
- In an absolute sense, all agonists are partial; selectivity for R_a over R_i cannot be total.

Antagonism

- A drug that binds with equal affinity to either conformation will not alter the activation equilibrium and will act as a competitive antagonist of any compound, agonist or antagonist, that does.
- A drug with preferential affinity for R_i actually will produce an effect opposite to that of an agonist; examples of such ***inverse agonists*** at G protein-coupled receptors (GPCRs) do exist (***e.g.,*** ***famotidine***, ***losartan***, ***metoprolol,*** and ***risperidone***).



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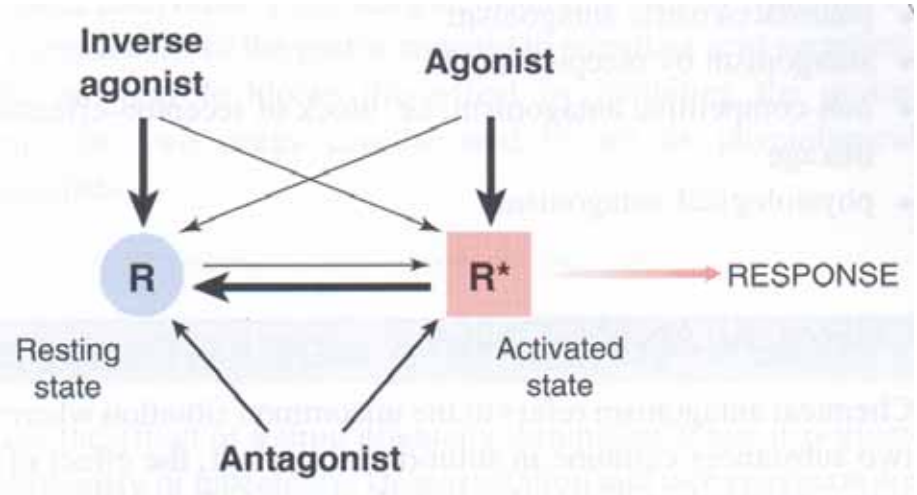

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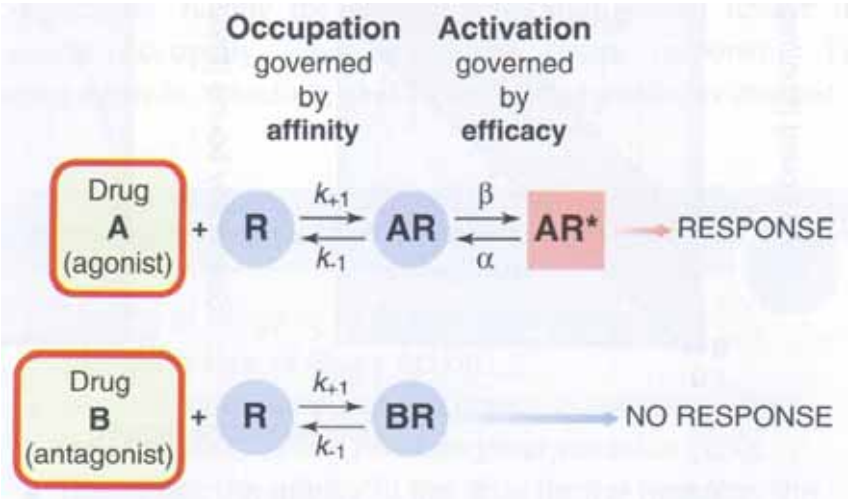

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Receptor types

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Type 1. Ligand-gated ion channels

- These receptors are located at the membrane. Their celular effects are mediated via ion channels coupled directly (e.g. Na^+, K^+, Ca^{2+}, Cl^- channels).
- Effect occurs in miliseconds.
- Examples: nicotinic acetylcholine receptors, $GABA_A$ receptor, NMDA receptor.

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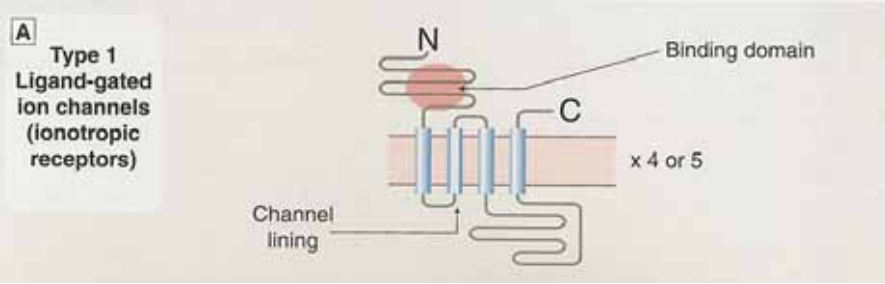
Ligand-gated ion channels



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Type 2. G-protein coupled receptors (GPCR)

- **These receptors are located at the membrane. Their celular effects are mediated via G-protein coupled second messengers.**
- **Effect occurs in seconds.**
- **Examples: muscarinic acetylcholine receptors, adrenergic receptors, $GABA_B$ receptor, metabotropic glutamate receptor.**

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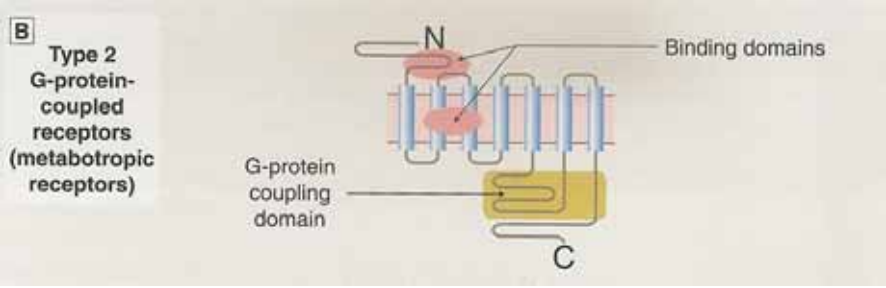
G-protein-coupled receptors



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Effectors controlled by G-proteins I

- Two key pathways are controlled by receptors, via G-proteins. Both can be activated or inhibited by pharmacological ligands, depending on the nature of the receptor and G-protein.
- Adenylate cyclase (AC)/cAMP:
  - —AC catalyses formation of the intracellular messenger cAMP
  - —cAMP activates various protein kinases, which control cell function in many different ways by causing phosphorylation of various enzymes, carriers and other proteins.

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Effectors controlled by G-proteins II

- Phospholipase C/inositol trisphosphate (IP_3)/diacylglycerol (DAG)
  - —catalyses the formation of two intracellular messengers, IP_3 and DAG, from membrane phospholipid
  - —IP_3 acts to increase free cytosolic Ca^{2+} by releasing Ca^{2+} from intracellular compartments
  - —increased free Ca^{2+} initiates many events, including contraction, secretion, enzyme activation and membrane hyperpolarisation
  - —DAG activates protein kinase C, which controls many cellular functions by phosphorylating a variety of proteins.

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Effectors controlled by G-proteins III

- Receptor-linked G-proteins also control:
  - —phospholipase A (and thus the formation of arachidonic acid and eicosanoids)
  - —ion channels (e.g. potassium and calcium channels, thus affecting membrane excitability, transmitter release, contractility, etc.).

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G proteinleri ile kenetli reseptörlere örnekler			
G proteini	**Efektör molekül**	**Etki**	**Reseptörler örnekler**
G_{i1}, G_{i2}, G_{i3}	Adenilat siklaz inhibisyonu, K^+ kanallarının açılması	cAMP ↓, hiperpolarizasyon	M_2, M_4, α_2-adrenerjik, D_2, D_3, D_4, δ-opioid
G_{olf}	Adenilat siklaz stimulasyonu	cAMP ↑	Koku (olfaktor epitel)
G_s	Adenilat siklaz stimulasyonu	cAMP ↑	β-adrenerjik, D_1, D_5, H_2, glukagon, ACTH, TSH
G_q	Fosfolipaz C stimulasyonu	IP_3, DAG ve Ca^{2+} ↑	M_1, M_3, M_5, α_1-adrenerjik, H_1, 5-HT_{1C}, bombesin
G_{t1}, G_{t2}	cGMP'ye spesifik fosfodiesteraz stimulasyonu	cGMP ↓	Fotonlar (retinada görme süreçleri, fototransdüksiyon, rodopsin)
G_o	Henüz belli değil	İnhibisyon	Bazı muskarinik (beyinde nörotransmitter)

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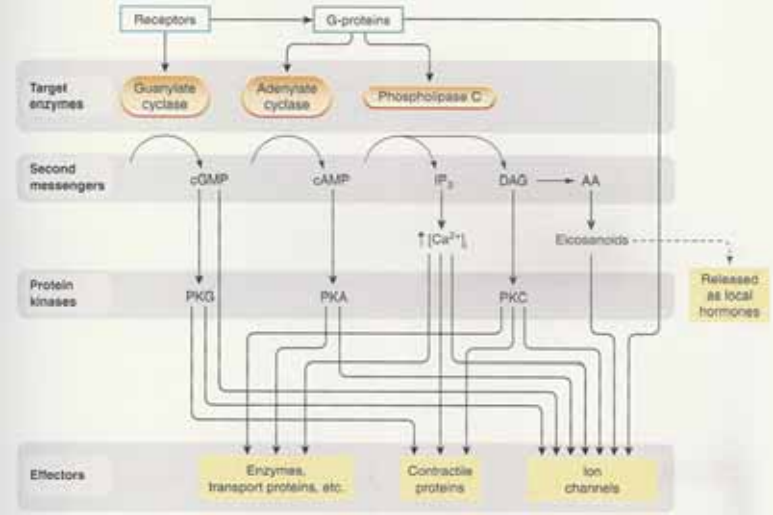
G-protein coupled celular events



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Type 3. kinase-linked receptors

- These receptors are located at the membrane. Their celular effects are mediated via tyrosine kinase or guanylate cyclase.
- Effect occurs in minutes (sometimes in hours).
- **Examples:** Tyrosine kinase-linked, insulin receptor, cytokine and growth factor (e.g. epidermal and platelet derived growth factors) receptors; guanylate cyclase linked, atrial natriuretic factor (ANF) receptor.
- Guanylate cyclase related events are mediated via protein kinase G (PKG).

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Tyrosine kinase mediated second messengers

- **Insulin receptor (when activated tyrosine kinase initiates various celular events and intracelular cAMP decreases)**
- **Ras/Raf/Mek/MAP kinase pathway is stimulated via growth factors which are important for cell division and differentiation**
- **Jak/Stat pathway is stimulated via cytokines which are responsible for synthesis and release of many inflammatory mediators**

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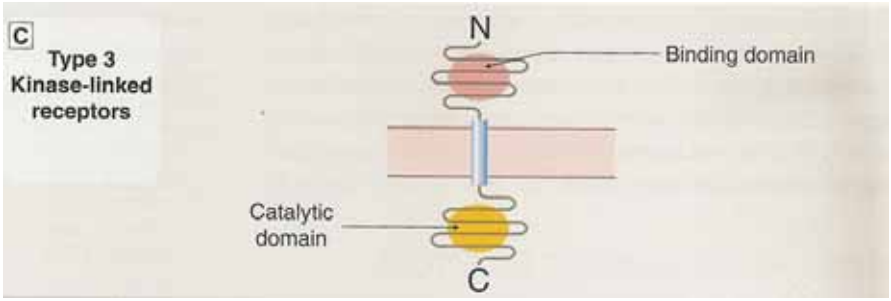
Kinase-linked receptors



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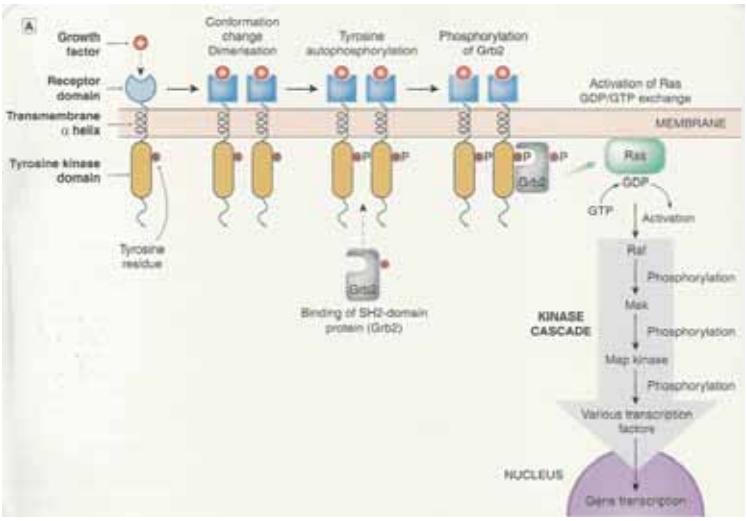
Growth factor (Ras/Raf) pathway



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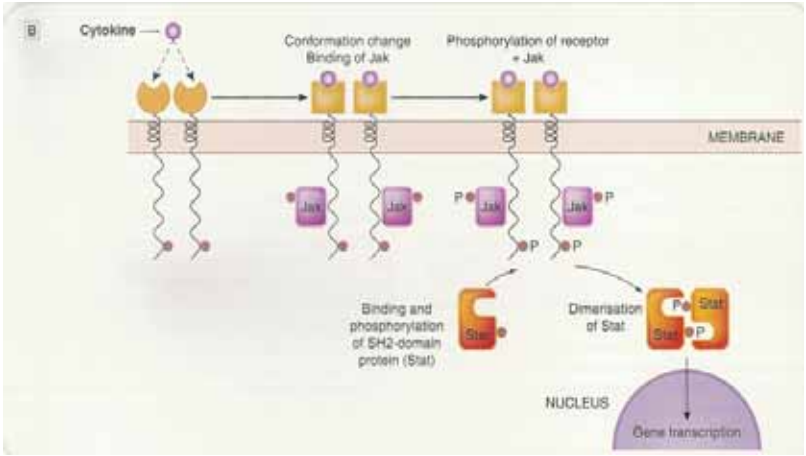
Cytokine (Jak/Stat) pathway



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Type 4. Cytoplasmic or nuclear receptors

- Steroid hormon, vitamine D and retinoic acid receptors are located at the cytoplasm. These hormons effect on gene transcription on DNA via (heat shock proteins, HSP).
- Tyroid hormon receptors are located at the nucleus.
- Effect depends on new protein synthesis and occurs in hours.
- Synthesis of effector proteins controlled via complex control cascades.

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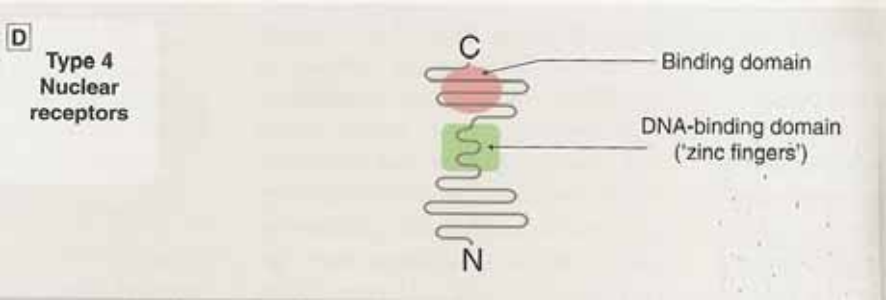
Steroid receptors



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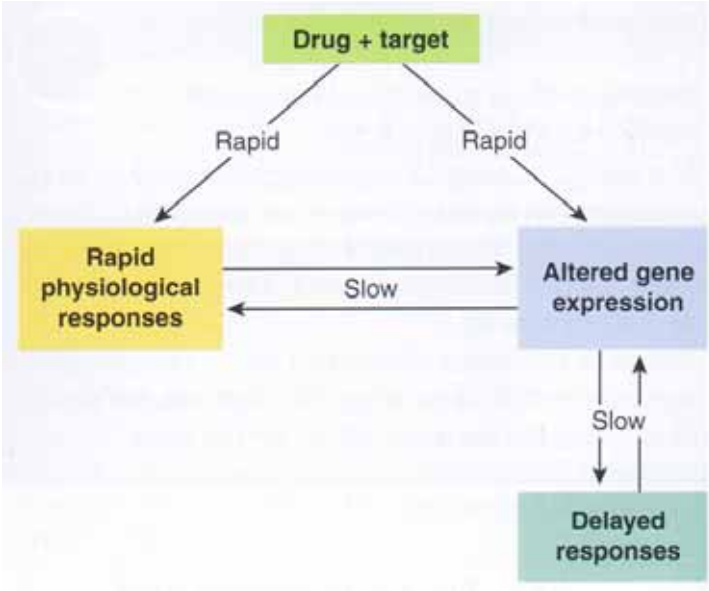

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Hücre membranına bağlanan ilaçların ve endojen maddelerin hücre içi etki mekanizmalarına örnekler

Adenilat siklaz/cAMP sistemini kullananlar

cAMP düzeyini arttıranlar

- Adrenokortikotropik hormon (ACTH)
- β-agonistler
- D_1-, D_2-agonistler
- Folikül stimule edici hormon (FSH)
- Glukagon
- Histamin (H_2)
- İnsan koryonik gonadotropini (HCG)
- Kalsitonin
- Kortikotropin salgılatıcı hormon (CRH)
- Lipotropin (LPH)
- Lutenizan hormon (LH)
- Melanosit stimule edici hormon (MSH)
- Paratiroid hormon (PTH)
- Serotonin ($5\text{-}HT_4$, $5\text{-}HT_6$, $5\text{-}HT_7$)
- Tiroid stimule edici hormon (TSH)
- V_2-reseptör agonistleri (ADH)

cAMP düzeyini azaltanlar

- α_2-agonistler
- D_3-, D_4-, D_5-agonistler
- M_2-, M_4-agonistler
- Opioidler
- Serotonin ($5\text{-}HT_1$)
- Somatostatin

Guanilat siklaz/cGMP sistemini kullananlar

- Atrial natriüretik peptit (ANP)
- Nitrik oksit (NO)

IP_3 diaçilgliserol sistemini kullananlar

- α_1-agonistler
- $5\text{-}HT_2$
- Anjiotensin II (AT_1)
- Bombesin
- Gonadotropin salgılatıcı hormon (GnRH)
- Histamin (H_1)
- Kolesistokinin
- M_1-, M_3- ve M_5-agonistler
- Oksitosin
- P maddesi
- Tirotropin salgılatıcı hormon (TRH)
- Trombosit aktive edici faktör (PAF)
- V_1-reseptör agonistleri (ADH)

Kinaz veya fosfataz sistemlerini kullananlar

- Atrial natriüretik faktör (ANF)
- Büyüme hormonu (GH)
- Epidermal büyüme faktörü (EGF)
- Fibroblast büyüme faktörü (FGF)
- İnsülin, insülin benzeri büyüme faktörü 1 (IGF-1)
- Koryonik somatomammotropin
- Prolaktin
- Sinir büyüme faktörü (NGF)
- Trombosit kaynaklı büyüme faktörü (PDGF)

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Hücre membranına bağlanan ilaçların ve endojen maddelerin hücre içi etki mekanizmalarına örnekler

Adenilat siklaz/cAMP sistemini kullananlar

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- Luteinizan hormon (LH)
- Melanosit stimule edici hormon (MSH)
- Paratiroid hormon (PTH)
- Serotonin ($5\text{-}HT_4$, $5\text{-}HT_5$, $5\text{-}HT_6$, $5\text{-}HT_7$)
- Tiroid stimule edici hormon (TSH)
- V_2-reseptör agonistleri (ADH)

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Guanilat siklaz/cGMP sistemini kullananlar

- Atrial natriüretik peptit (ANP)
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IP_3 diaçilgliserol sistemini kullananlar

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- Koryonik somatomammotropin
- Prolaktin
- Sinir büyüme faktörü (NGF)
- Trombosit kaynaklı büyüme faktörü (PDGF)

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Dose-response relationship

- **Quantal dose-response relationship: Effect of drug is "all or none" (action is either present or absent).**
- **Graded dose-response relationship: Effect of drug is enhanced with increasing concentration/dosage.**

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American Journal of Pharmaceutical Education **2004; 68 (3) Article 73.**

TEACHERS' TOPICS

Teaching Pharmacodynamics: An Introductory Module On Learning Dose-Response Relationships

Kenneth A. Skau, PhD

College of Pharmacy, University of Cincinnati

The introductory pharmacodynamics course entitled, *Principles of Pharmacology*, was designed as an active-learning exercise to help students discover basic pharmacology principles associated with dose—response curves and drug-receptor interactions. Autonomic drugs were used to illustrate many of the principles. Rather than use pure lecture format, the instructor led students through a discovery process to understand the principles. During the learning process students were encouraged to develop both lower-order and higher-order learning processes. An example is presented here in which a simulated treatment of fever with an antipyretic demonstrates progressive development of a quantal distributional plot, a quantal cumulative dose-response curve, and a continuous cumulative dose-response curve, and the use of log dose to enhance data presentation.

Keywords: Pharmacodynamics, dose-response, drug-receptor interaction, Socratic teaching, pharmacology

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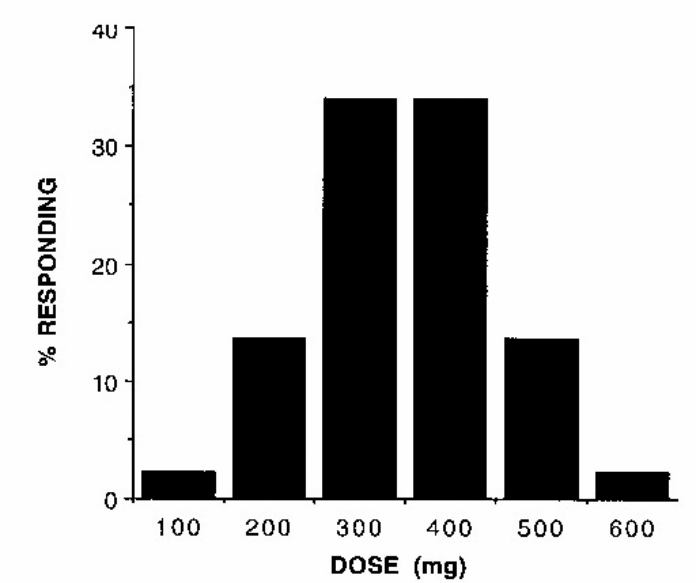

Figure 1. Noncumulative, quantal dose-response relationship.

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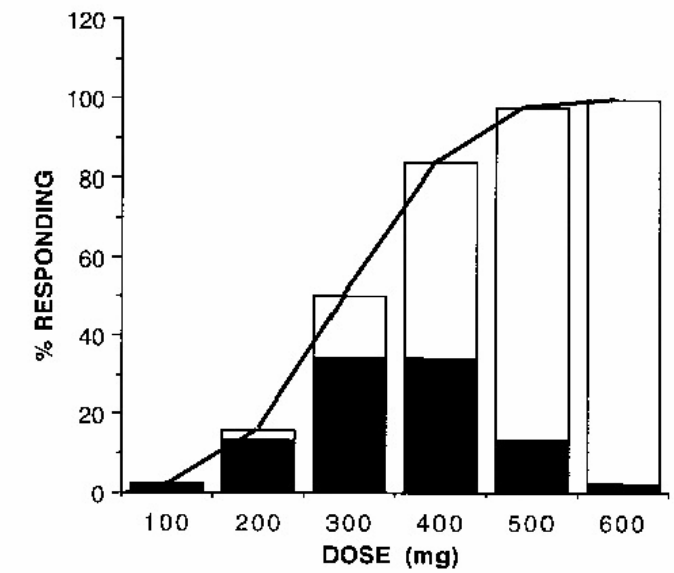

Figure 2. Cumulative, quantal dose-response relationship.

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Table 2. Data for Log Dose-Response Curve

Histamine, mM	Response, %
0.0001	0.5
0.0003	2.25
0.001	18.5
0.003	32.0
0.01	78.0
0.03	91.0
0.1	96.0
0.3	100.0

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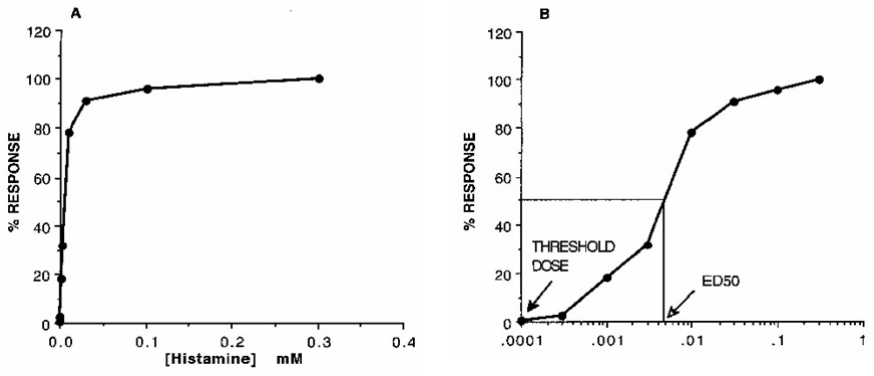

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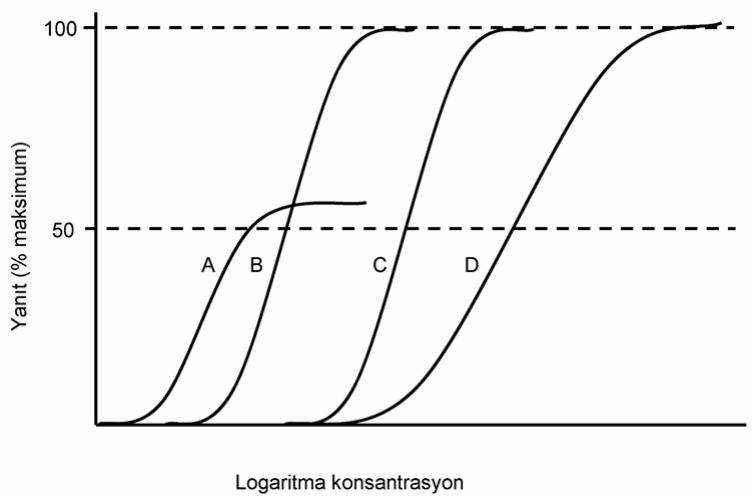
Graded dose-response relationship



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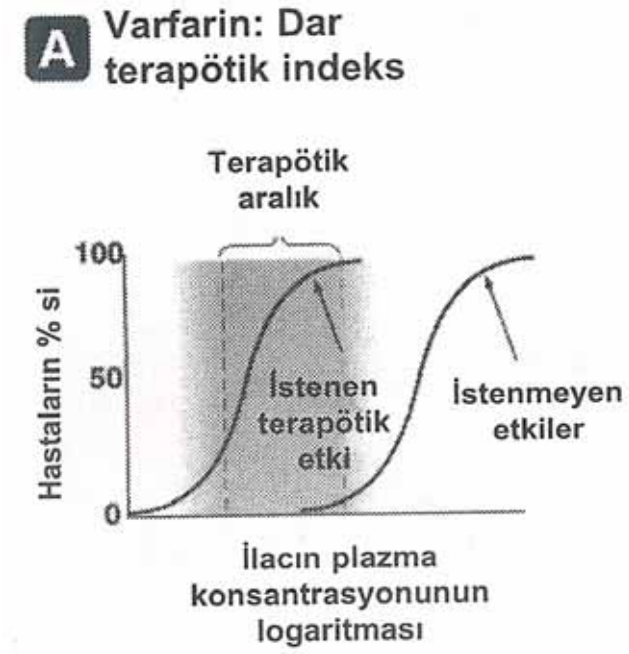
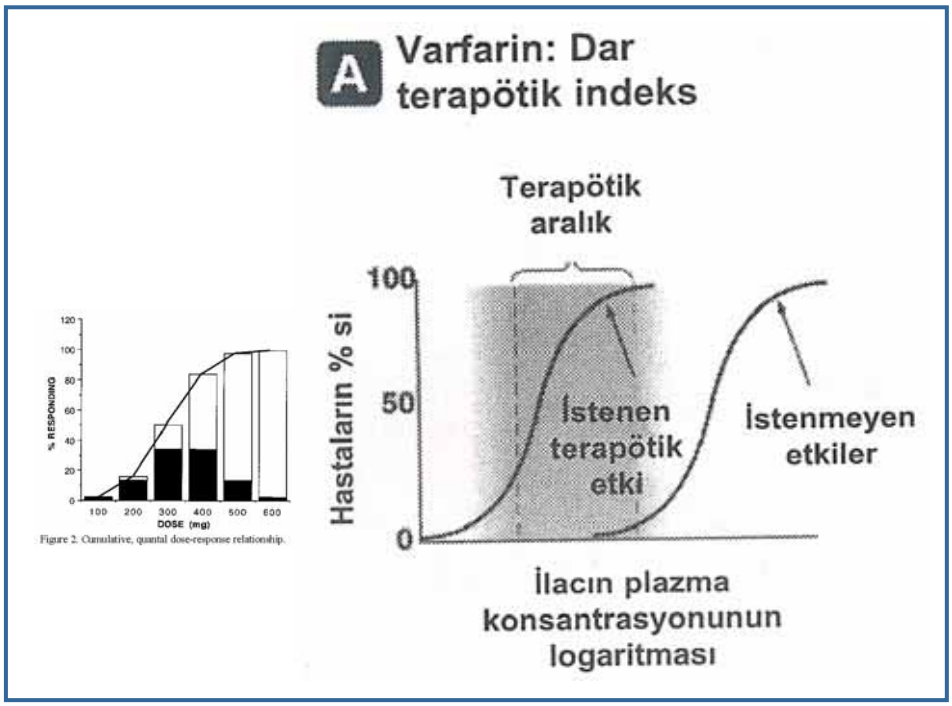
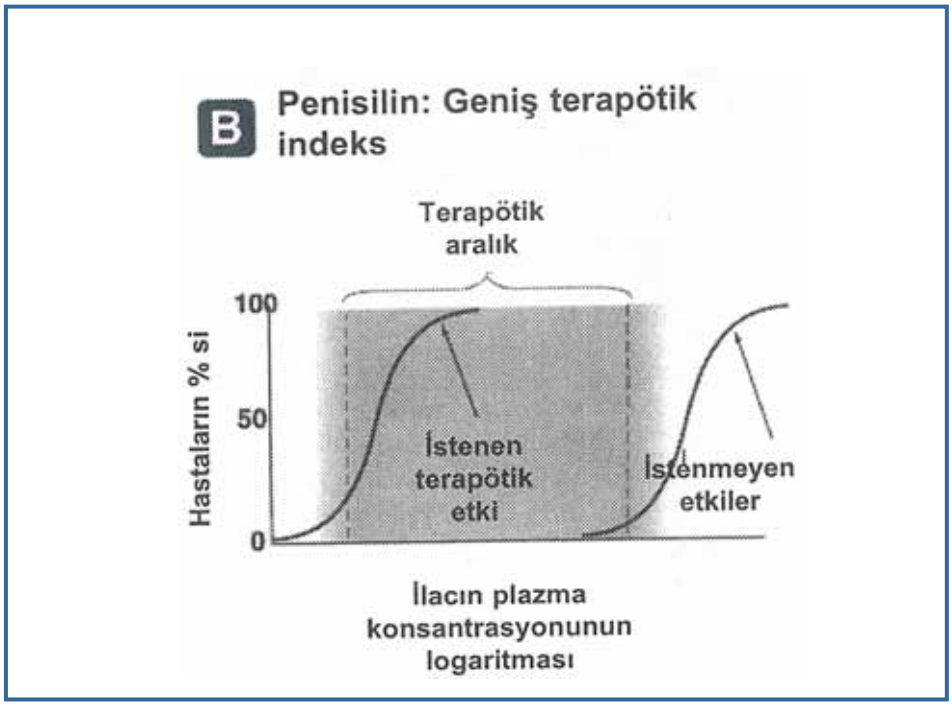



A
Varfarin: Dar terapötik indeks
Terapötik aralık
100
50
0
Hastaların % si
İstenen terapötik etki
İstenmeyen etkiler
İlacın plazma konsantrasyonunun logaritması
% RESPONDING
DOSE (mg)
Figure 2. Cumulative, quantal dose-response relationship.


B
Penisilin: Geniş terapötik indeks
Terapötik aralık
100
50
0
Hastaların % si
İstenen terapötik etki
İstenmeyen etkiler
İlacın plazma konsantrasyonunun logaritması

Drug antagonism

- **Chemical antagonism:** Antagonist binds to agonist and deactivates/neutralizes. Most of the chemical antagonists are antidotes.
- **Pharmacological antagonism:** Agonist and antagonist effects directly or indirectly on the same receptor. It can be competetive or non-competetive.
- **Physiological antagonism:** Antagonist effects on a physiological mechanism that is antagonist to the pathway that agonist effects.
- **Pharmacokinetic antagonism:** Interaction of antagonist on absorption, distribution, metabolism, and elimination (ADME) of agonist.

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Farmakolojik antagonizma için örnekler	
İlaç	**Farmakolojik antagonisti**
Atropin	Fizostigmin
Benzodiazepinler	Flumazenil
Histamin	Antihistaminikler
Muskarinik ilaçlar, asetilkolin esteraz inhibitörleri	Atropin
Narkotik analjezikler	Nalokson
Nondepolarizan nöromüsküler blokerler	Asetilkolin esteraz inhibitörleri
Sempatomimetik vazokonstriktörler	α-adrenerjik reseptör blokerleri

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Fizyolojik antagonizma için örnekler	
İlaç	**Fizyolojik antagonisti**
Amfetamin	Klorpromazin, β-blokerler
Barbitüratlar ve narkotik analjeziklerle solunum depresyonu	Kafein, doksapram
β-blokerler	Glukagon, atropin
Efedrin, fenilpropanamin, tiraminin noradrenalin salıverici etkileri	α-metiltirozin
Konvulsif maddeler	Diazepam, volatil anestetikler
Noradrenalin ve benzeri vazokonstriktörler	Kolin esterleri, nitratlar, histamin
Propranolol ve furosemidin antihipertansif etkileri	Aspirin, indometasin
Trisiklik antidepresanlar	Fizostigmin

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Parsiyel agonistlere örnekler

- Asebutolol, alprenolol, pindolol (β-reseptörler)
- Dihidroksiergokristin, ergotamin (α-reseptörler)
- Nalorfin (opioid reseptörler)
- Tamoksifen (östrojen reseptörü)

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Quantifying antagonism

- Characteristic patterns of antagonism are associated with certain mechanisms of blockade of receptors. One is simple ***competitive antagonism***, whereby a drug that lacks intrinsic efficacy but retains affinity competes with the agonist for the binding site on the receptor. The characteristic pattern of such antagonism is the concentration-dependent production of a parallel shift to the right of the agonist dose-response curve with no change in the maximal asymptotic response.
- Competitive antagonism is surmountable by a sufficiently high concentration of agonist.
- The magnitude of the rightward shift of the curve depends on the concentration of the antagonist and its affinity for the receptor. The affinity of a competitive antagonist for its receptor therefore can be determined according to its concentration-dependent capacity to shift the concentration-response curve for an agonist rightward, as analyzed by Schild (1957).

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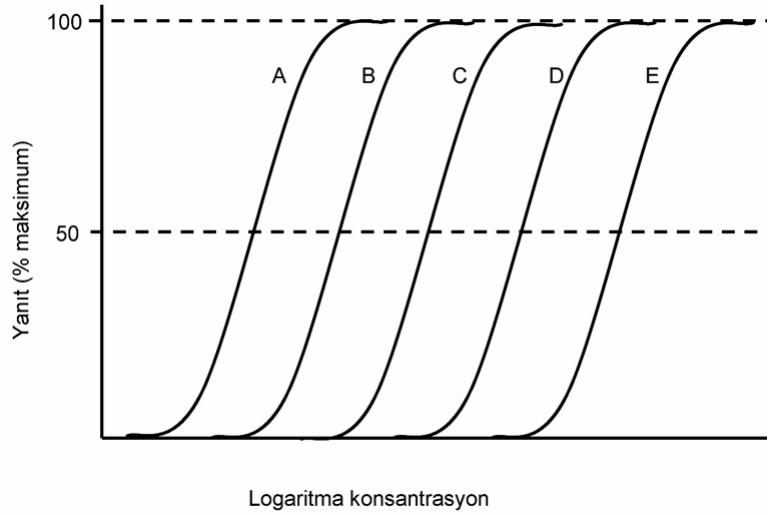
Reversible competitive antagonism I



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Reversible competitive antagonism II

- **Dose Ratio (r):**

The ratio=

agonist concentration (dose) required to produce a given response (effect) in the presence of an antagonist

agonist concentration (dose) required to produce the same response in the absence of an antagonist

- **Schild plot (regression):** **When logarithm of antagonist concentration (logC) is plotted on X axis, and log(r-1) on Y axis, all points are on the same line. The line meets X axis when dose ratio is 2 (i.e. log(2-1)=0). The antagonist concentration at this point is called K_B.**
- **K_B: The antagonist concentration that makes dose ratio 2 (a constant value).**

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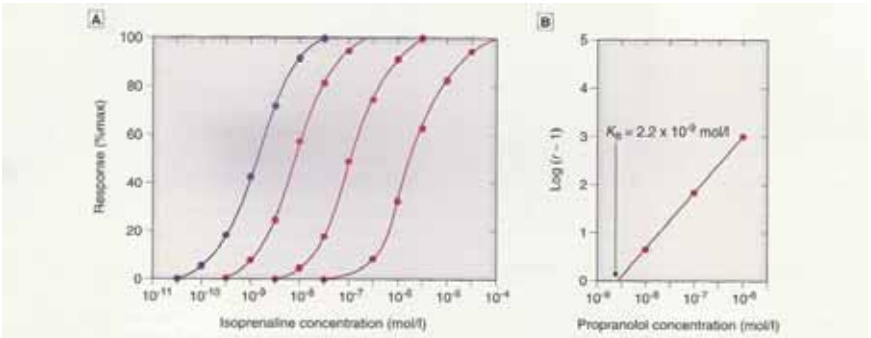

Fig. 2.8 Competitive antagonism of isoprenaline by propranolol measured on isolated guinea pig atria. A Concentration–effect curves at various propranolol concentrations (indicated on the curves). Note the progressive shift to the right without a change of slope or maximum. B Schild plot (equation 2.10). The equilibrium constant (K) for propranolol is given by the abscissal intercept 2.2×10^{-9} mol/l. (Results from Potter L T 1967 J Pharmacol 155: 91.)

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Reversible competitive antagonism III

- pA_2= -logK_B It determines the afinity of antagonist to a given receptor.
  The pA_2 value is constant for a competetive antagonist binding to the same receptor subtype on different tissues.
- pA_{10}= -logX_{10} (X_{10} is the antagonist concentration that makes dose ratio 10).
- At competitive antagonism: $pA_2 - pA_{10} = \log(9) = 0.95$

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Noncompetitive antagonism I

- An antagonist may dissociate so slowly from the receptor as to be essentially irreversible in its action. Under these circumstances, the maximal response to the agonist will be depressed at some antagonist concentrations.
- Operationally, this is referred to as *noncompetitive antagonism,* although the molecular mechanism of action really cannot be inferred unequivocally from the effect.

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Noncompetitive antagonism II

- **Noncompetitive antagonism can be produced by another type of drug, referred to as an *allosteric antagonist*. This type of drug produces its effect by binding a site on the receptor distinct from that of the primary agonist and thereby changing the affinity of the receptor for the agonist. In the case of an allosteric antagonist, the affinity of the receptor for the agonist is decreased by the antagonist.**
- **In contrast, some allosteric effects could potentiate the effects of agonists. The interaction of benzodiazepines (anxiolytics) with the $GABA_A$ receptor to increase the receptor's affinity for GABA is an example of allosteric potentiation.**

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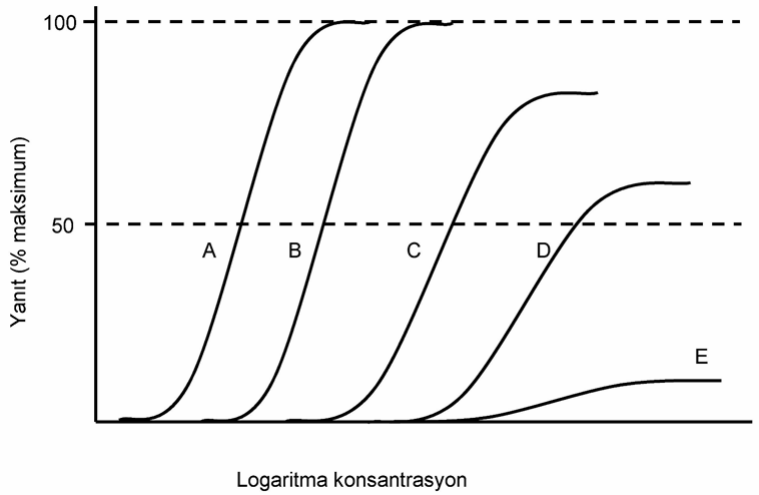
Noncompetitive antagonism III



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Desensitization and tachyphylaxis

- Continued stimulation of cells with agonists generally results in a state of *desensitization* (also referred to as *adaptation, refractoriness,* or *down-regulation*) such that the effect that follows continued or subsequent exposure to the same concentration of drug is diminished.
- This phenomenon known as *tachyphylaxis* occurs rapidly and is very important in therapeutic situations; an example is attenuated response to the repeated use of β receptor agonists as bronchodilators for the treatment of asthma.

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Thank you

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