Pharmacodynamics

Pharmacodynamics

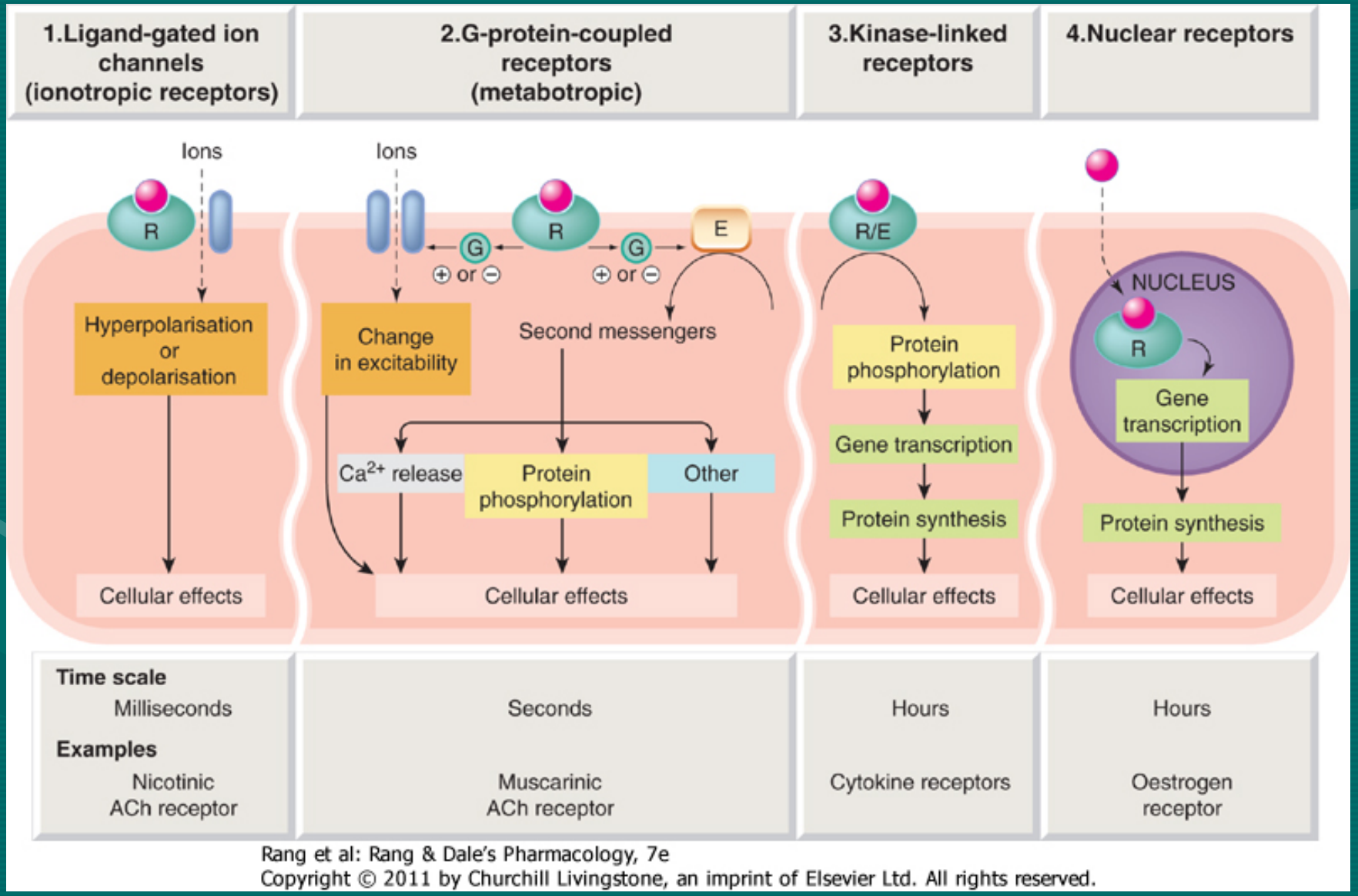
- Receptor: macromolecule or the component of a cell or organism that interacts with a drug and initiates the chain of biochemical events leading to the drug's observed effects
  - Found in target cells or tissues
  - Determine the dose or concentration of drug required to form a significant # of drug-receptor complexes.
  - # of receptors may limit maximal effect a drug may produce
  - Responsible for selectivity of drug action
    - Size, shape, electrical charge of drug determines binding to a receptor
    - Changes in a drug's chemical structure can alter the affinity for the receptor where therapeutic and toxic effects may be altered
  - Receptors mediate the actions of pharmacologic antagonists

Pharmacodynamics

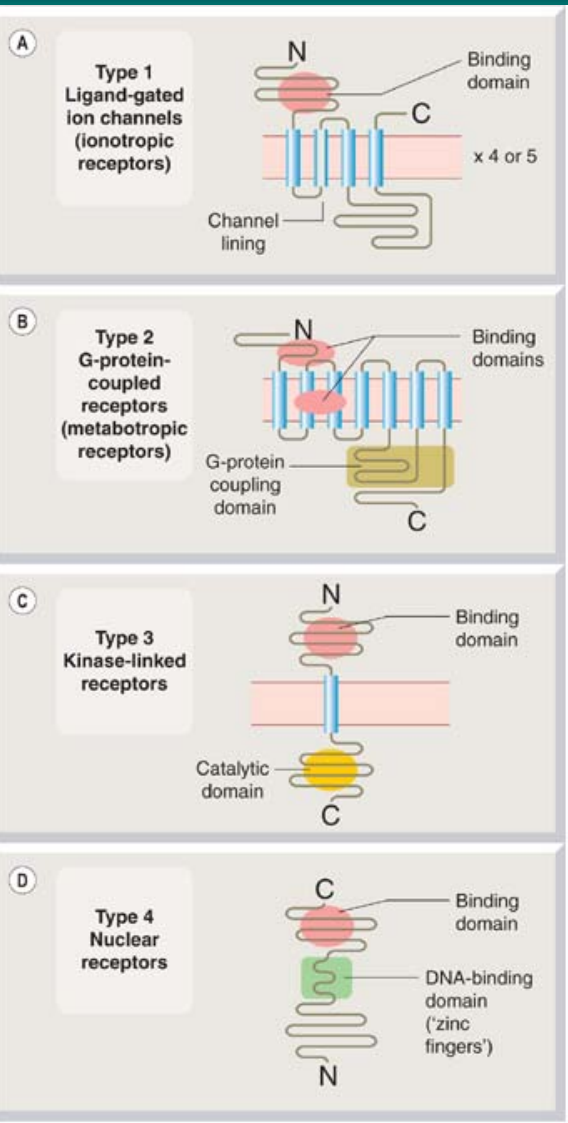
- Types of Receptors

- Most receptors are cellular proteins whose normal function is to act as receptors for endogenous regulatory ligands – particularly hormones, growth factors, and neurotransmitters
- Regulatory proteins – mediate the actions of endogenous chemical signals such as neurotransmitters, autacoids, and hormones
  - This class of receptors mediates the effects of many of the most useful therapeutic agents
- Enzymes – receptors that are inhibited by binding a drug
  - Ex: dihydrofolate reductase – receptor for methotrexate
- Transport proteins
  - Ex: Na+/K+ ATPase, membrane receptor for digoxin
- Structural proteins
  - Ex: tubulin, the receptor for colchicine

Receptor Types



Receptor structures



Ion-channel-linked receptors

There are two general classes of ion channels: voltage-gated and ligand-gated. Voltage-gated ion channels are activated by alterations in membrane voltage. For example, voltage-gated sodium (Na^+) channels open when the membrane is depolarized to a threshold potential and contribute to further membrane depolarization by allowing Na^+ influx into the cell.

Ligand-gated ion channels are activated after binding to specific ligands or drugs. Many neurotransmitters and drugs activate membrane- bound ligand ion -gated channels, including several types of glutamate receptors

G-protein-linked receptors

G-protein-linked receptors compose a large class of membrane-bound receptors. The protein structure of these receptors includes a common seven-membered transmembrane domain. In general, receptors linked to G proteins greatly amplify the biologic signal because they activate G proteins, which in turn activate ion channels or, more commonly, other enzymes (e.g., adenylate cyclase), leading to stimulation of still other enzymes (e.g., protein kinase A)." This amplification system, which generally involves an extended duration of activation of the G protein relative to the binding of drug to the receptor, may explain why maximal pharmacologic effects are often observed when only a small proportion of receptors are activated

Enzyme-linked receptors

Enzyme-linked receptors have only one transmembrane domain_per protein subunit,with "an enzymatic catalytic site on the cytoplasmic side of the receptorgy. Dimerization of activated receptors provides the confirmational change required for expression of enzymatic activity. The catalytic sites are commonly protein kinases that phosphorylate tyrosine,

Intracellular receptors

Lipophilic substances capable of crossIng the plasma membrane may activate intracellular receptors: Sex steroids, mineralocorticoids, glucocorticoids, and thyroid hormones all activate specific intracellular receptors

Pharmacodynamics

- Five basic mechanisms of transmembrane signaling
  - 1. A lipid soluble ligand (agonist, drug) crosses the membrane and acts on an intracellular receptor
    - Ex: nitric oxide (NO)
    - Ex: corticosteroids, mineral corticoids, sex steroids, vitamin D, and thyroid hormone
      - Used to regulate gene expression
      - In the nucleus, receptor binds to specific DNA sequences near the gene
      - Therapeutic consequences:
        - All of the above hormones produce their effect after 30 minutes to several hours (time required for new protein synthesis)
        - The drug will not relieve symptoms right away
        - Ex: Glucocorticoids should not be the drug used for acute bronchial asthma

Pharmacodynamics

- Five basic mechanisms of transmembrane signaling
  - 1. **A lipid soluble ligand (drug) crosses the membrane and acts on an intracellular receptor**
    - Ex: corticosteroids, mineral corticoids, sex steroids, vitamin D, and thyroid hormone
      - Therapeutic consequences (cont):
        - Effects of these drugs can last hours or days even when drug has been stopped. Reason – relatively slow turnover of most enzymes or proteins. After being synthesized, they will remain active in cell for hours or days
  - 2. **Ligand binds to the extracellular domain of the transmembrane receptor activating enzymatic activity of it's cytoplasmic domain**

Pharmacodynamics

- Five basic mechanisms of transmembrane signaling
  - 3. **Ligand binds to the extracellular domain of the transmembrane receptor which in turn is bound to and activates tyrosine kinase in the cytoplasm**
    - Ex of ligands: insulin, EGF (epidermal growth factor), PDGF (platelet-derived growth factor), ANF (atrial natriuretic factor), and TGFβ (transforming growth factor-β)
    - ANF – regulates blood volume and vascular tone. Intracellular receptor binding domain guanylyl cyclase → cGMP
    - TGFβ – Intracellular receptor binding domain serine kinase

Pharmacodynamics

- Five basic mechanisms of transmembrane signaling
  - 3b. **Cytokine receptors**
    - Ligands bind to the extracellular domain of the transmembrane receptor which is bound noncovalently to and activates a separate protein tyrosine kinase, from the Janis Kinase family
    - Ex of ligands: growth hormone, interferons, erythropoietin
    - Tyrosine residues are phosphorylated
    - STAT (signal transducer and activator of transcription) is phosphorylated
    - STAT dimerization and dissociation from receptor
    - Dimer travels to nucleus and regulates transcription of specific genes

Pharmacodynamics

- Five basic mechanisms of transmembrane signaling
  - 4. **Ligand binds to and directly regulates the opening and closing of a transmembrane ion channel**
    - Ex of ligands: acetylcholine, GABA, excitatory amino acids: glycine, aspartate, glutamate (synaptic neurotransmitters)
    - Rapid signaling mechanism
    - Ex of drug: neuromuscular blocking agents like benzodiazepines or barbiturates

Pharmacodynamics

- Five basic mechanisms of transmembrane signaling
  - 5. **Ligand binds to a transmembrane receptor linked to an effector (enzyme or ion channel) by a G-protein**
    - Ex of ligands: serotonin, adrenergic amines, muscarinic acetylcholine, peptide hormones, odorants, photons
    - Effector increases conc. of 2nd messanger (cAMP, Ca++, etc..)
      - Ex: Effector enzyme adenylyl cyclase converts ATP to cAMP
    - Duration of activation of adenylyl cyclase depends on longevity of GTP binding to G protein rather than receptors affinity for drug (like norepinephrine)
    - The slow hydrolysis of GTP causes the active G protein to persist long after the receptor has dissociated from its agonist molecule. Receptors will appear to be spare
    - (Table 2-2) Family of G-proteins
      - Each mediates effects of a particular set of receptors to a distinctive group of effectors
    - All receptors coupled to G-proteins are structurally related and called "serpentine receptors" → means receptor polypeptide chain crosses plasma membrane 7 times
      - G proteins interact with AA in the 3rd cytoplasmic loop of receptor polypeptide

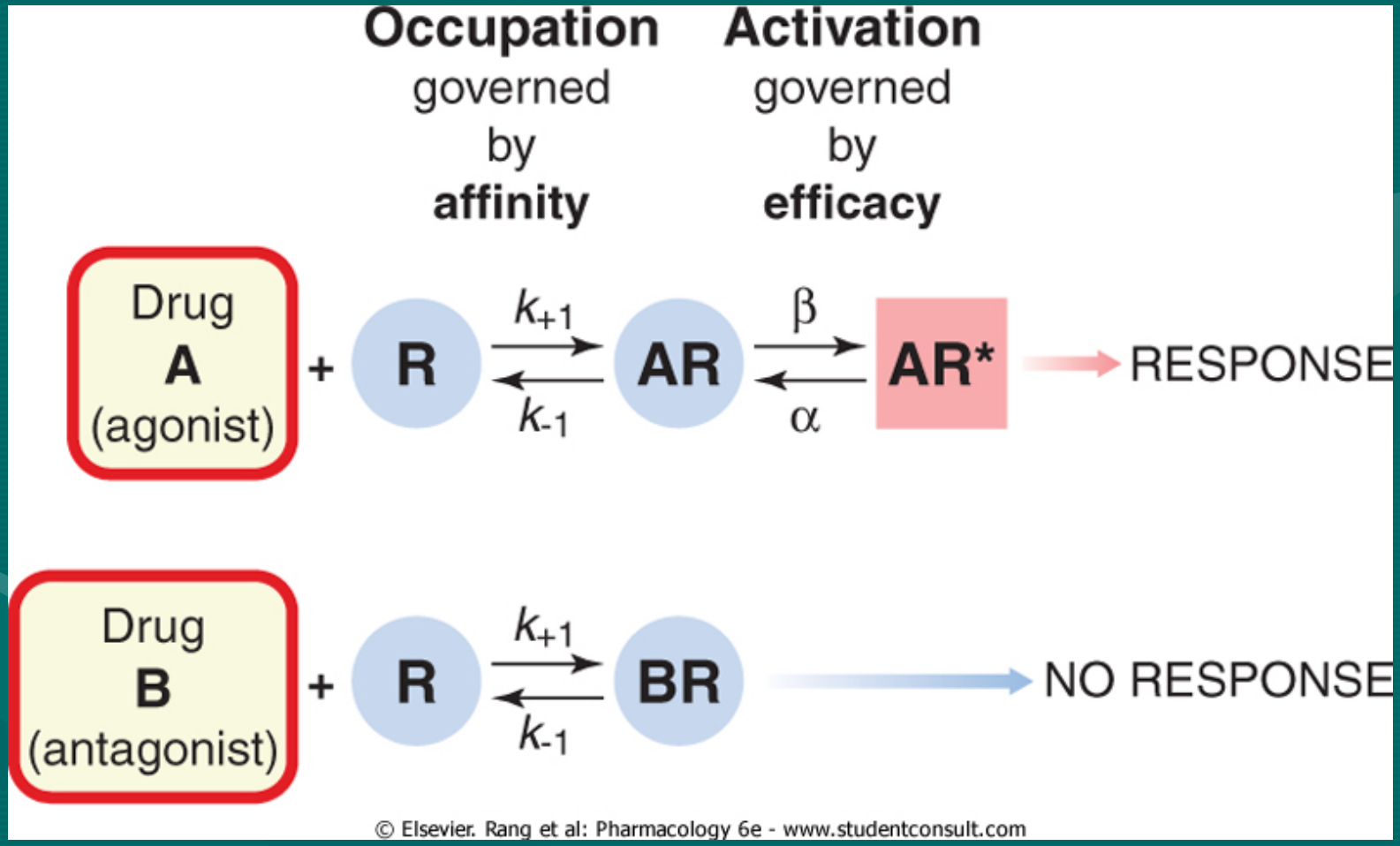
Drug-Receptor Interactions

Theory and assumptions of drug-receptor interaction

- Combination or binding to receptor causes some event which leads to the response.
- Response to a drug is graded or dose-dependent.
- Drug receptor interaction follows simple mass-action relationships, i.e., only one drug molecule occupies each receptor site and binding is reversible.
- For a given drug, the magnitude of response is directly proportional to the fraction of total receptor sites occupied by drug molecules (i.e. the occupancy assumption).
- The number of drug molecules is assumed to be much greater than the number of receptor sites.

- Combination of drug with a receptor produces a specific response. "lock and key".
- Drug-receptor interactions are analogous to enzyme-substrate interactions. Most of the same principles apply.
- Endogenous ligands (e.g. enkephalin versus morphine).
- Drugs without specific receptors (e.g. gaseous anesthetics).

The distinction between drug binding and receptor activation



- Drug-receptor interactions with characteristics outlined above can be treated with an equation analogous to the Michaelis Menten equation utilized for enzyme-substrate interactions.

$$D + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} DR \xrightarrow{k_3} \text{Effect}$$

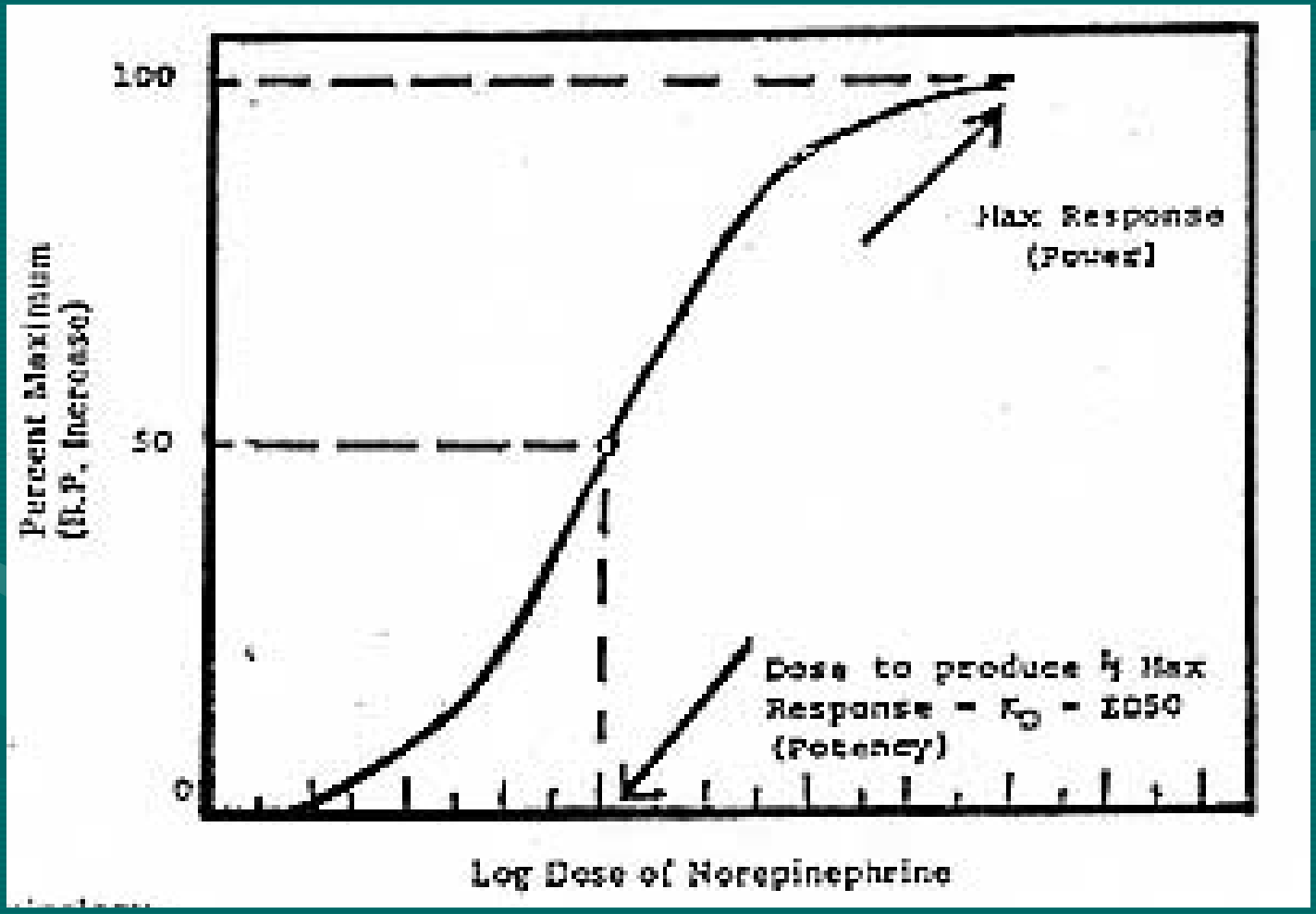
- Hill-Langmuir equation

$$p_A = \frac{x_A/K_A}{x_A/K_A + 1} \qquad (2.5)$$

The Log Dose-Response Curve

- Advantages of expression as log versus response
  - Dose-response relationship expressed as a nearly straight line over a large range of drug doses.
  - Wide range of doses can be plotted on a single graph, allowing easy comparison of different drugs.
  - Use of log dose-response curves to compare different drugs which produce the same response

Typical log dose-response curve



Pharmacodynamics

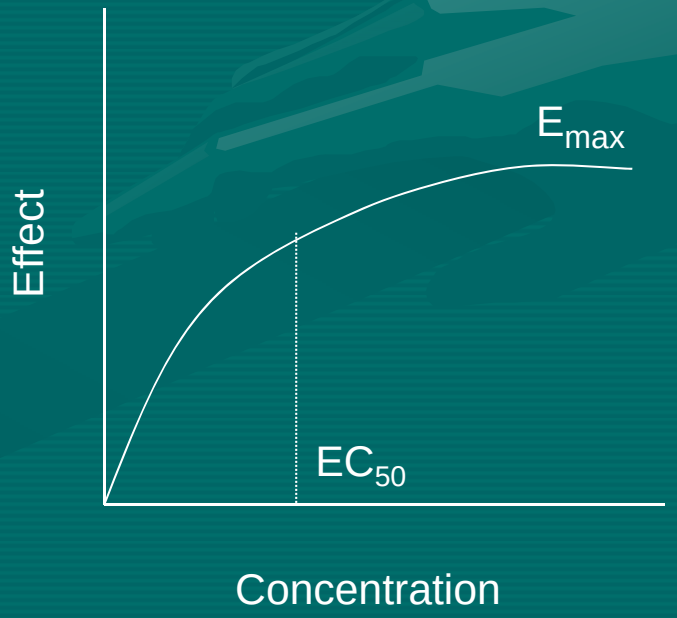
- Three aspects of drug-receptor function
  - 1. Receptors determine the quantitative relation between drug concentration and response
    - This is based on receptor's affinity to bind and it's abundance in target cells or tissues
    - Drug response depends on:
      - Affinity of drug for receptor
      - Drugs efficacy (degree to which a drug is able to induce maximal effects)
  - 2. Receptors (as complex molecules) function as regulatory proteins and components of chemical signaling mechanisms that provide targets for important drugs
  - 3. Receptors determine the therapeutic and toxic effects of drugs in patients

Pharmacodynamics

- Drug concentration-effect curve

- E_{max}- – maximal response that can be produced by the drug
- EC_{50} – conc. of drug that produces 50% of maximal effect
- Responses to low doses of a drug usually in direct prop. to dose
- As a dose 's, it reaches a point at which no in response can be achieved

- At a low concentration, effect is changing rapidly
- At a high concentration, effect is changing slowly

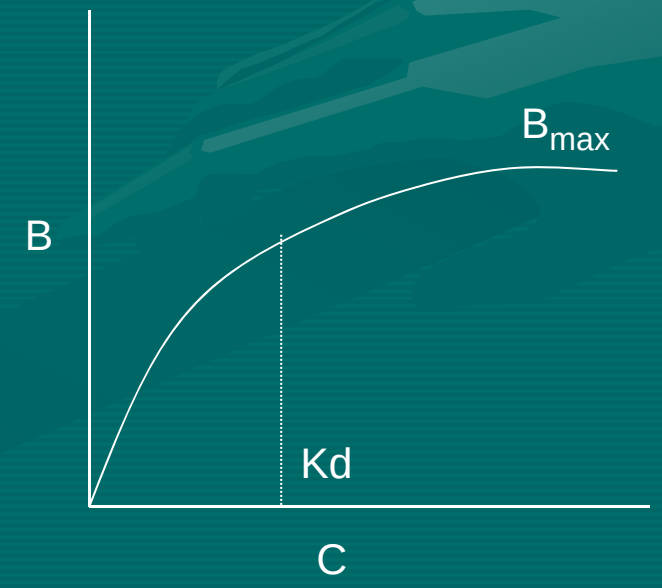


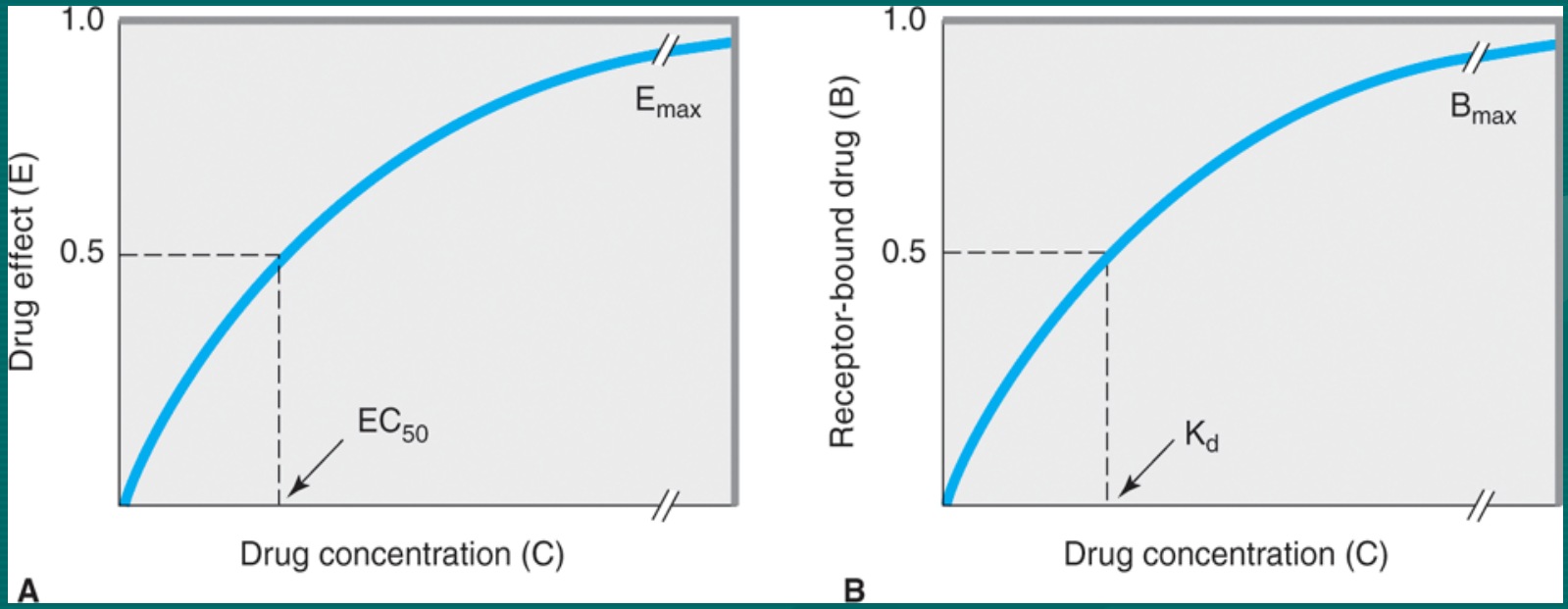
Pharmacodynamics

- Drug concentration-receptor bound curve

- B – drug bound to receptors
- C – concentration of free (unbound) drug
- Kd – the concentration of free drug at which half-maximal binding is observed (characterizes the binding affinity of receptor for drug)
- B_{max} – total concentration of receptor sites (at high concentration of drug)

- If Kd is low, binding affinity is high





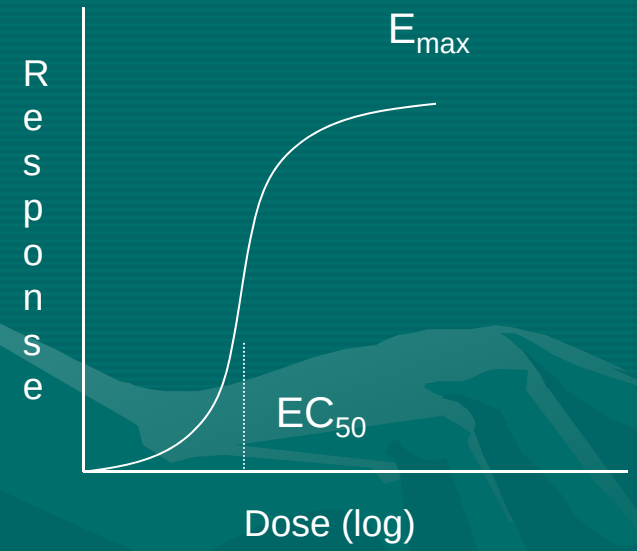
Relations between drug concentration and drug effect (panel A) or receptor-bound drug (panel B). The drug concentrations at which effect or receptor occupancy is half-maximal are denoted EC_{50} and K_d, respectively.

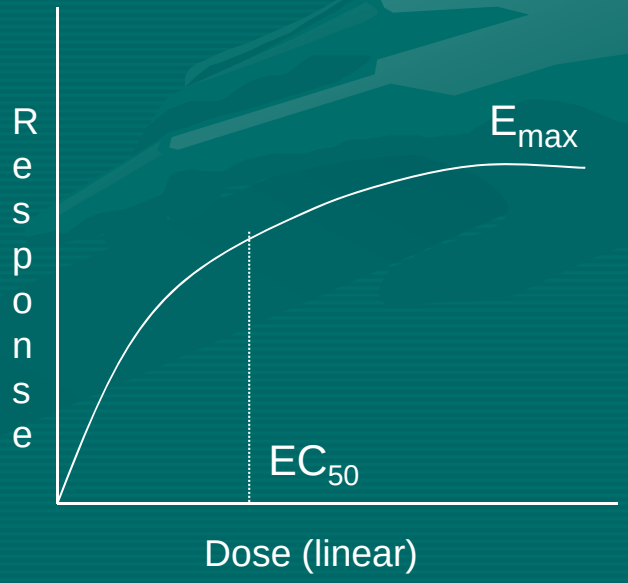
Pharmacodynamics

- Relation between drug dose and clinical response
  - Want to give a dosage regimen that will produce maximal benefit and minimal toxicity
  - **Graded Dose Response**
    - Measures potency of a drug and efficacy of a drug
    - Potency – the amt of drug needed to produce a given effect
      - The lower the dose needed to produce a response, the more potent the drug. The smaller the EC_{50}, the > the potency of the drug.
      - Is determined mainly by:
        - Affinity of receptor for the drug
        - Efficiency with which drug-receptor interactions is coupled to response
      - Want a drug to be low in potency if administering in inconveniently large amts
    - Clinical effectiveness – depends on maximal efficacy and drugs ability to reach the relevant receptors
      - Depends on route, absorption, distribution, and clearance of drug
    - Efficacy – the largest response or maximal effect (E_{max}) a drug can produce
      - Is determined mainly by:
        - The nature of the receptor and its associated effector system
        - Drugs mode of interaction with receptors
      - Partial agonist have lower maximal efficacy than full agonists

Pharmacodynamics

- Graded Dose-Response Curves



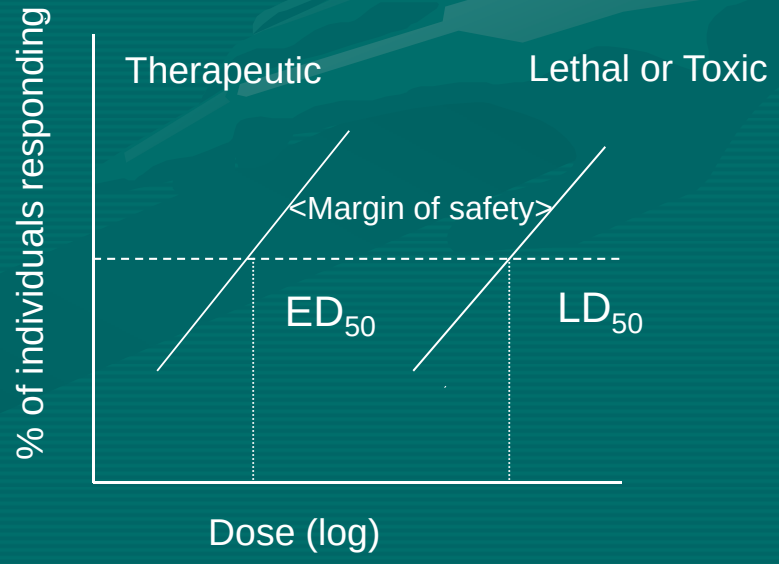


Pharmacodynamics

- **Quantal (either-or) dose response**

- Considers variability among patients in severity of disease and responsiveness to drugs
- Measures the effect (response) in a large # of individual patients at various doses
- Measures and compares the potencies of drugs
- Therapeutic index – relates the dose of a drug required to produce a desired effect to that which produces an undesired effect
- T.I. = $\frac{LD_{50}\text{(lethal dose in 50\%)}}{ED_{50}\text{(effective dose in 50\%)}}$

- A high therapeutic index indicates that the drug produces the desired effect at a dose that is rarely lethal; there is a large margin of safety



Pharmacodynamics

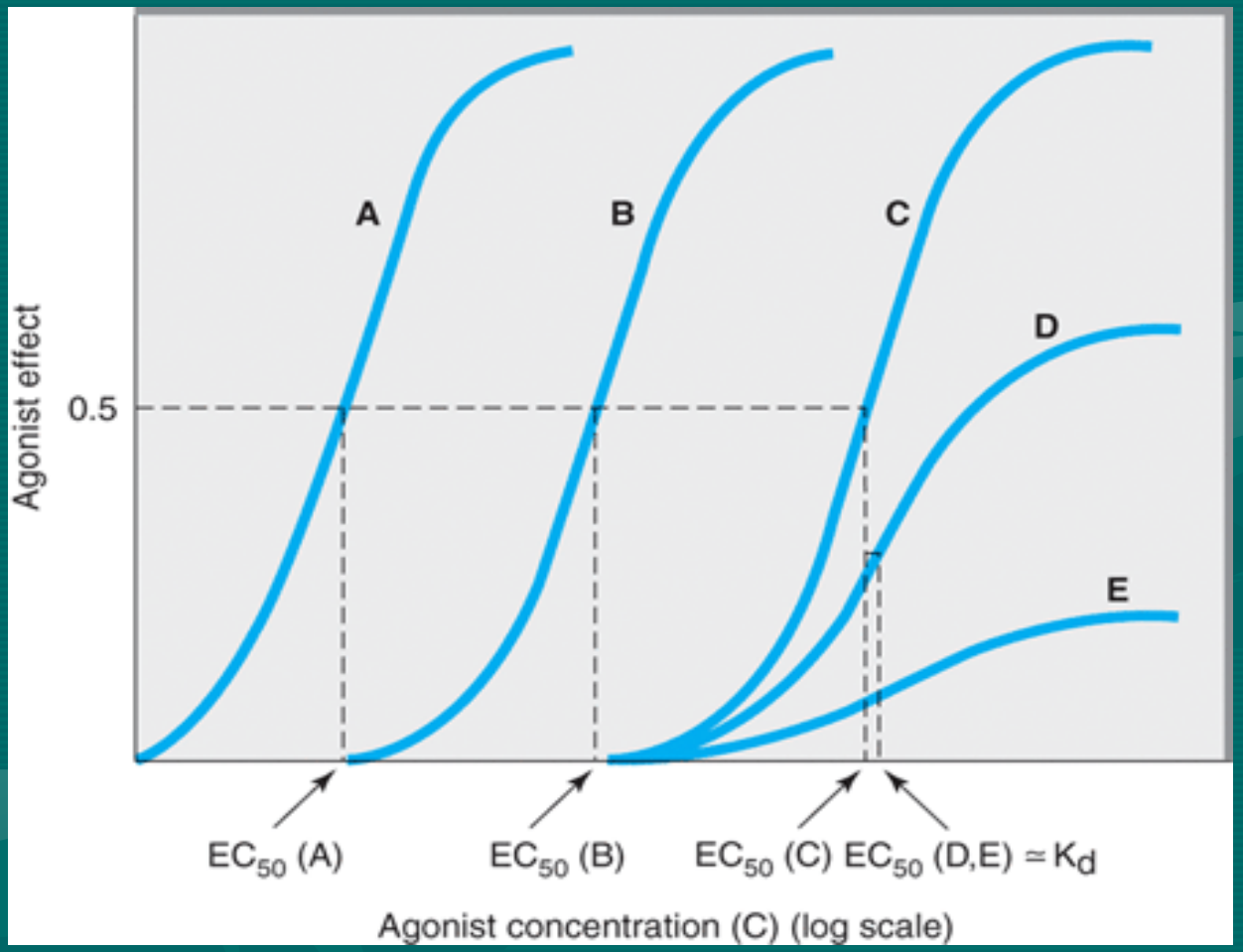
- Receptor-effector coupling

- Transduction process between receptor occupancy and drug response
  - Effector – receptor cellular target
  - Coupling – products of one reaction become reactants in another
  - Transduction – transfer of information from one cell to another. Conversion of energy from one form to another
- Coupling efficiency is determined by:
  - 1. initial conformational change in receptor
  - 2. biochemical events that transduce receptor occupancy into cellular response

Pharmacodynamics

- Spare receptors – unoccupied receptors
  - Maximal response can be achieved by an agonist even if a fraction of receptors (spare receptors) are unoccupied
    - Maximal drug response (the response you want) only requires so many receptors
  - Sensitivity of cell to the agonist concentration depends on affinity of receptor for drug, in addition to, *total receptor concentration*
    - With more receptors available, the chance of binding is greater
  - There are spare receptors if the concentration of drug that produces 50% of the maximum effect (EC_{50}) is less than the concentration of free drug at which 50% of maximum binding is observed (Kd)
  - Reasons for having spare receptors:
    - 1. the effect of the drug-receptor interaction may last longer than the interaction itself
    - 2. the # of receptors may exceed the # of effector molecules available

Experimental demonstration of spare receptors, using different concentrations of an irreversible antagonist



Curve B,C,D,E show response to increasing concentration of irreversible antagonist. The apparent EC50 of the agonist in curves D and E may approximate the Kd that characterizes the binding affinity of the agonist for the receptor.

Pharmacodynamics

- Antagonists
  - Bind the receptor, do not activate it
  - Main effect – prevent agonists (other drugs or endogenous regulatory molecules) from binding and activating
  - Two classes:
    - 1. Competitive antagonists
      - Progressively inhibit agonist response
      - The degree of inhibition produced by a competitive antagonist depends upon the concentration of antagonist
        - High concentrations prevent response completely
      - Higher concentrations of agonist are required to produce the same effect of agonist alone

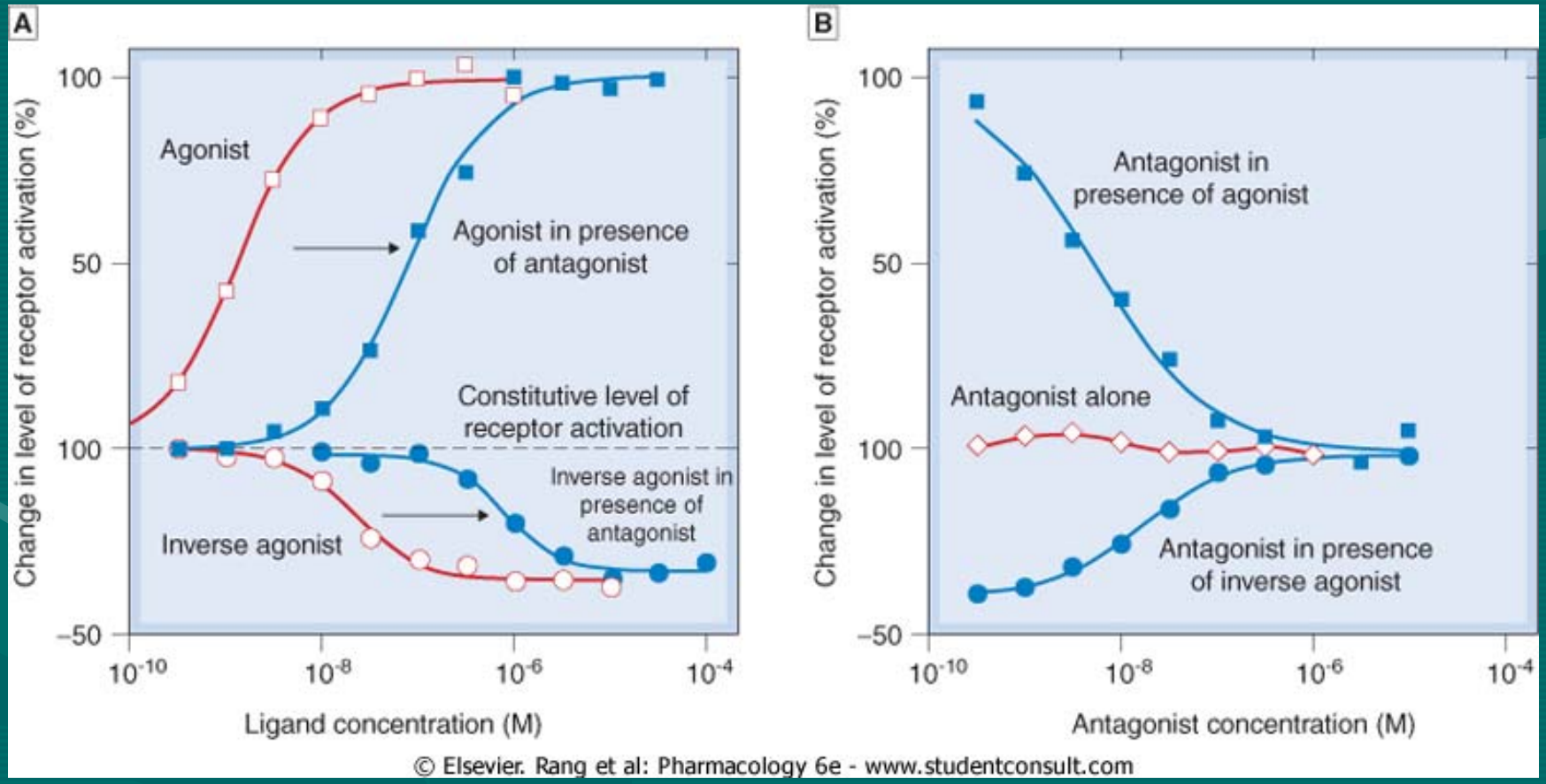
Pharmacodynamics

- Antagonists
  - Two classes:
    - 1. Competitive antagonists
      - Ex of concentration of endogenous agonist competing for binding site: Propranolol (β antagonist)
        - Doses sufficient to block the effect of norepinephrine will dec resting HR; however, exercise, postural change, or emotional stress will inc release of norepinephrine or epinephrine and may overcome competitive antagonism by propranolol and inc HR
    - 2. Irreversible antagonist
      - Binds covalently to receptor
      - Duration of action more dependent upon the rate of turnover of receptor molecules
      - Ex: Phenoxybenzamine (α antagonist)
        - Used to dec (control) blood pressure in pheochromocytoma (tumor of adrenal medulla)
        - Tumor will episodically release catecholamines which inc blood pressure
        - Do not use an overdose! Very dangerous

Pharmacodynamics

- Chemical antagonists
  - Do not require a receptor
  - One drug may bind to another drug and inactivate the drug and it's actions
    - Ex: Protamine (+ charge) will counteract effects of Heparin (- charge)
- Agonists
  - 1. Full agonists
  - 2. Partial agonists
    - Fails to produce maximal effects even if all receptor sites are occupied
    - Ex: Stadol® (butorphanol)
      - μ antagonist (lowers addiction) and k agonist (analgesic effect)
    - Weak partial agonists can seem to be like competitive antagonists

Inverse agonist



Pharmacodynamics

- Receptor regulation
  - Depends on receptor and duration of stimulation
  - With time, receptor-mediated responses to drugs or hormonal agonist reversibly ***desensitize***. After reaching an initial high level, the response gradually diminishes over seconds or minutes, even in the continued presence of the agonist. 15 minutes after the removal of the agonist, a second exposure to agonist results in a response similar to the initial response because internalized receptors are not degraded but instead return intact to the plasma membrane within several minutes
  - If receptor is continually stimulated (prolonged activation), the receptor will be delivered to lysosomes and undergo ***down regulation*** Ex: β adrenoceptors

Pharmacodynamics

- Receptor regulation (cont)
  - Down-regulation
    - Increases receptor internalization and degradation
    - Slower onset and more prolonged effect than desensitization
    - Occurs over hours or days
    - Is an agonist-induced decrease in the total # of cell-surface receptors
    - Intensity and duration of action of EGF, PDGF, and other agents that act via tyrosine kinase receptor are limited because of this process
    - Cells responsiveness to ligand is correspondingly diminished

Pharmacodynamics

- Variation in drug responsiveness
  - Individuals may vary considerably in their responsiveness to a drug
  - Idiosyncratic drug response – unusual, one that is infrequently observed in most patients
    - Caused by:
      - Genetic differences in metabolism
      - Immunologic mechanism (allergy)
  - Hyporeactive – intensity of effect is decreased
  - Hyperreactive – intensity of effect is increased
  - Hypersensitivity – allergic or other immunologic response to drugs resulting from previous sensitizing exposure
  - Tolerance – responsiveness usually decreases as a consequence of continued drug administration.
    - Need greater doses of a drug to produce original degree of effect as time progresses or need to substitute different drug
  - Tachyphylaxis – responsiveness diminishes rapidly after administration of a drug (the first few doses), very rapid tolerance

Pharmacodynamics

- Variation in drug responsiveness
  - Four general mechanisms:
    - **1.** Patients may differ in the rate of absorption of a drug, in distributing it through body compartments, or in clearing the drug from the blood which may alter the conc of drug that reaches receptor
      - This can be due to age, weight, sex, disease state, liver and kidney function, and genetic differences
    - **2.** Patients may vary in their concentrations of endogenous receptor ligand
      - Can vary in the response to pharmacologic antagonist
      - Ex: Propranolol (β blocker)
        - Pt with pheochromocytoma as opposed to healthy runner

Pharmacodynamics

- Variation in drug responsiveness
  - Four mechanisms (cont.)
    - **3**. Patients may have differences in the # of receptor sites or differ in the function of their receptors due to the efficiency of coupling receptor to effector
      - Drug Induced down-regulation
      - The "overshoot" phenomena
        - Antagonists – when discontinued, the elevated # of receptors can produce an exagerated response to physiologic conc of agonist
        - Agonist – when discontinued, # of receptors that have been dec by down regulation is too low for endogenous agonist to produce effective stimulation
        - Ex: Clonidine (α agonist) decreases blood pressure. When withdrawn, can produce hypertensive crisis. Pt will have to be weaned slowly
    - **4**. Patients vary in functional integrity of biochemical processes in the responding cell and physiologic regulation by interacting organ systems
      - Can be caused by age of pt or general health of pt. Most importantly, severity and pathophysiologic mechanism of the disease
  - Drug therapy will be most successful when there is correct diagnosis and if it is accurately directed at the pathophysiologic mechanism responsible for the disease

Concept of specific drug receptors

- Most drugs combine with specific sites on macromolecules (e.g. cell membrane components, enzymes, proteins) by precise physiochemical and steric interactions between specific chemical groups of the drug. These sites are termed **receptors.**

Terminology

- Terms which indicate ability of drug to produce a response
  - Efficacy
  - Power
  - Intrinsic Activity

    (Corresponds to Vmax in Michaelis-Menten analogy)

- Terms which indicate ability of drug to bind to receptor
  - Potency
  - Affinity
  - K_D or ED50
    (Corresponds to Km in Michaelis-Menten analogy)

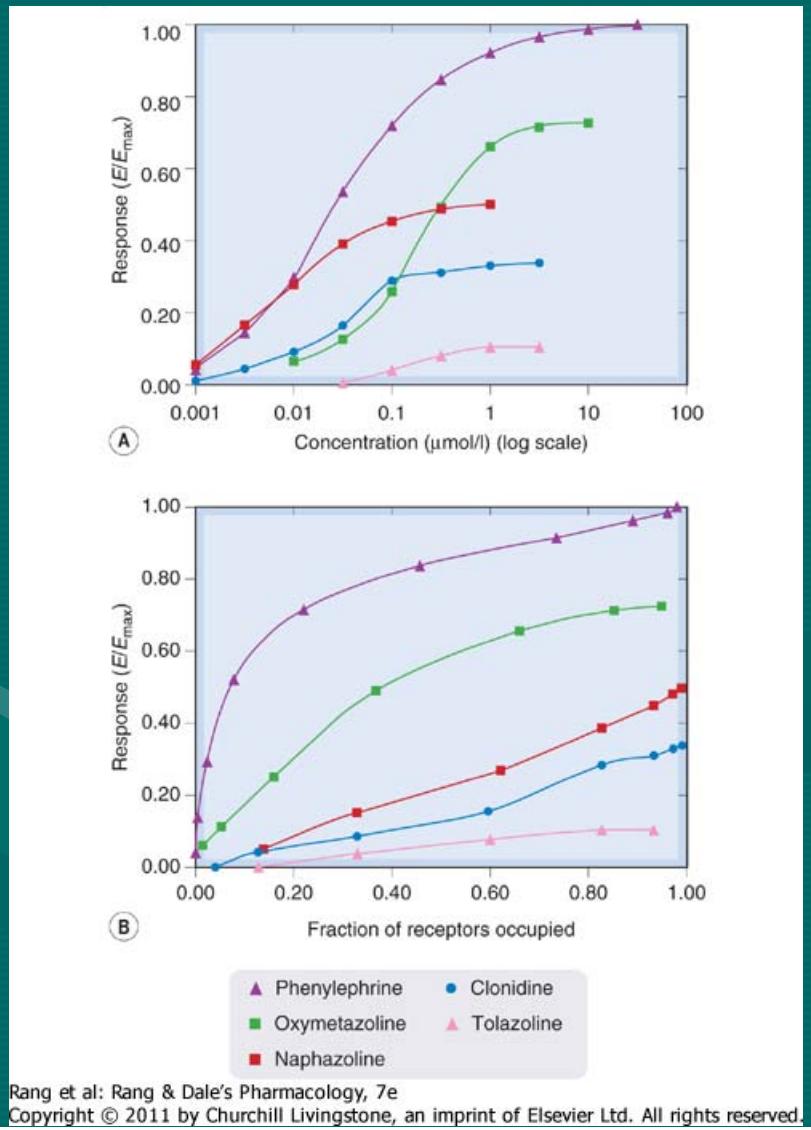
Agonists (or Full Agonists)

- **Drugs that occupy receptors and bring about a full or maximal response. The maximal response is usually defined as that produced by the most powerful agonists, or that produced by a drug associated classically with the response.**

Partial Agonists

- **Drugs that occupy receptors but bring about less than the maximum response. That is, these drugs are less powerful and 100% occupancy produces a lesser response (correspond to substrates with a lower Vmax in enzyme analogy).**

Partial agonists



- [**A**] Log concentration-effect curves for a series of α-adrenoceptor agonists causing contraction of an isolated strip of rabbit aorta. **Phenylephrine** is a full agonist. The others are partial agonists with different efficacies. [**B**] The relationship between response and receptor occupancy for the series. Note that the full agonist, phenylephrine, produces a near-maximal response when only about half the receptors are occupied, whereas partial agonists produce submaximal responses even when occupying all of the receptors. The efficacy of **tolazoline** is so low that it is classified as an α-adrenoceptor antagonist (see Ch. 14). In these experiments, receptor occupancy was not measured directly, but was calculated from pharmacological estimates of the equilibrium constants of the drugs. (Data from Ruffolo et al. 1979 J Pharmacol Exp Ther 209: 429-436.)

Antagonists

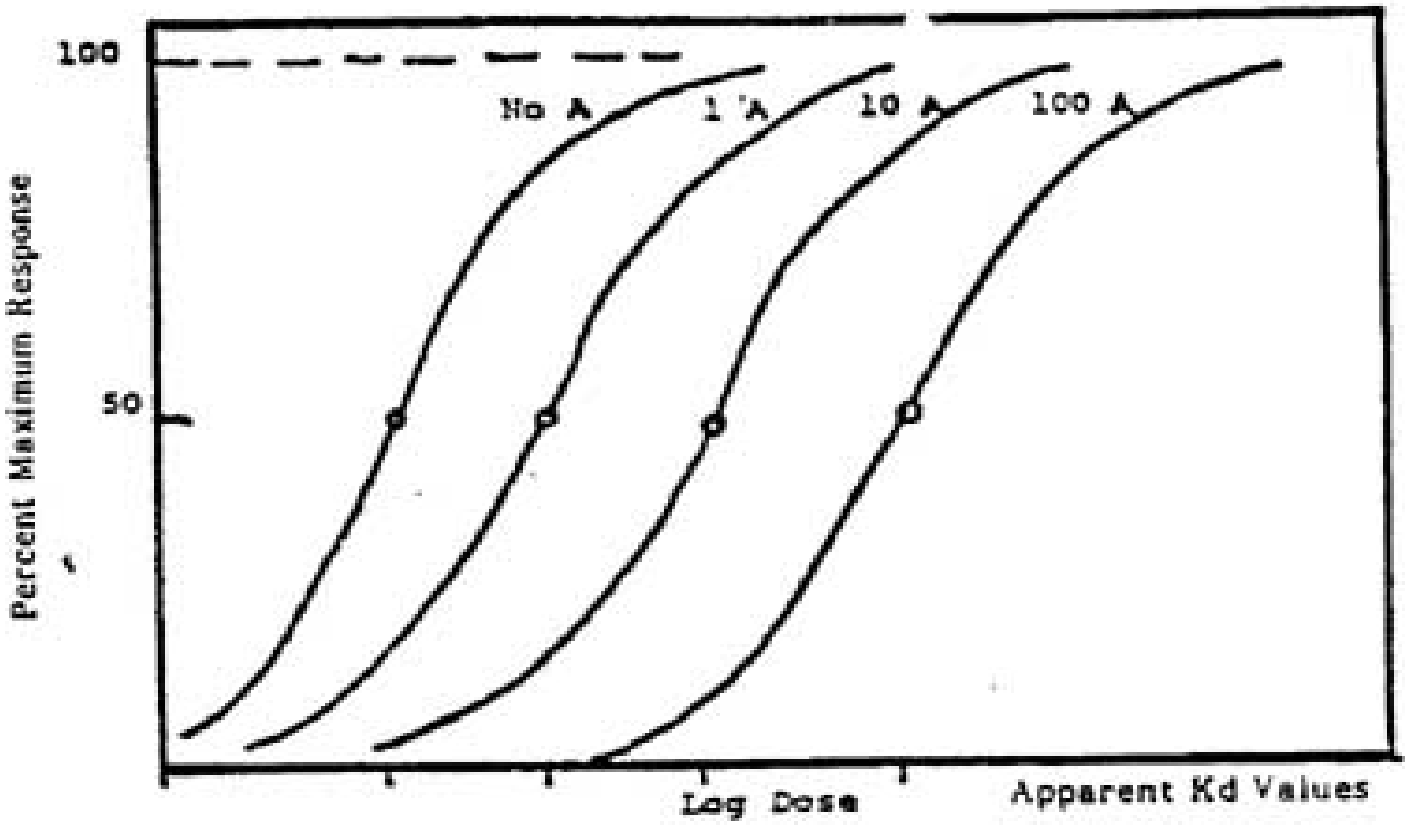
- **Drugs that occupy or change the receptor but do not bring about any response. Occupancy by an antagonist interferes with occupancy by a drug capable of causing a response**

General Types of Drugs Interactions

- **Antagonism, Pharmacological Competitive or Surmountable. The antagonist reversibly competes for or displaces the agonist from the receptor. Since occupancy by an antagonist produces no response, the action of the agonist is blocked. Higher concentrations of agonist, however, can overcome this competition and restore the full response. In the presence of a competitive antagonist, there is no change in maximal response; but the log dose-response curve is shifted towards higher concentrations of the drug.**

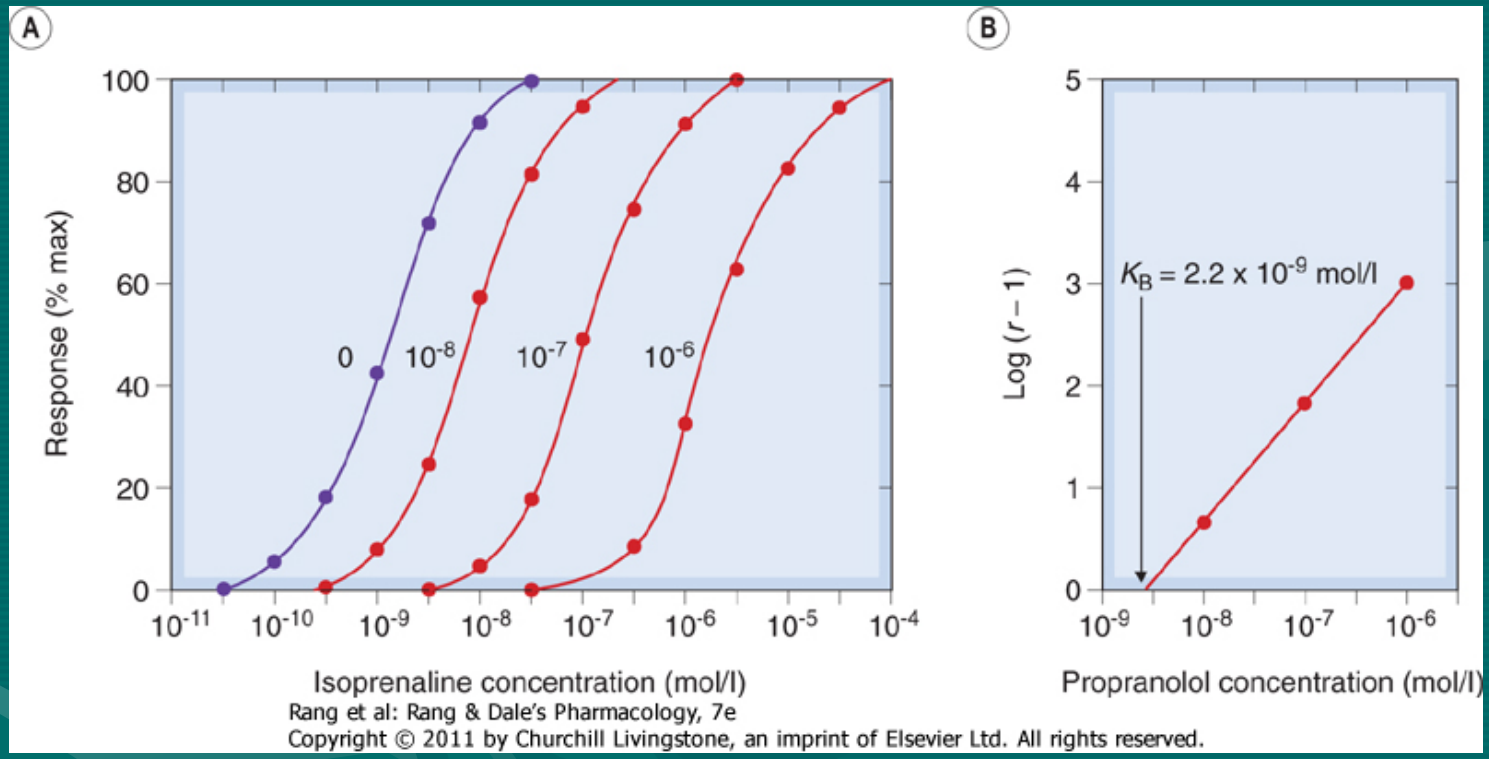
- the apparent potency of the drug is reduced in the presence of a competitive antagonist but power is unchanged. The effectiveness of a competitive antagonist depends on its affinity for the receptor site relative to the affinity of the agonist. The situation is exactly analogous to competitive inhibition of enzyme reactions, and similar mathematics apply.

Competitive Inhibition



Log dose-response curves for a drug in the presence of increasing amounts of a competitive antagonist, A

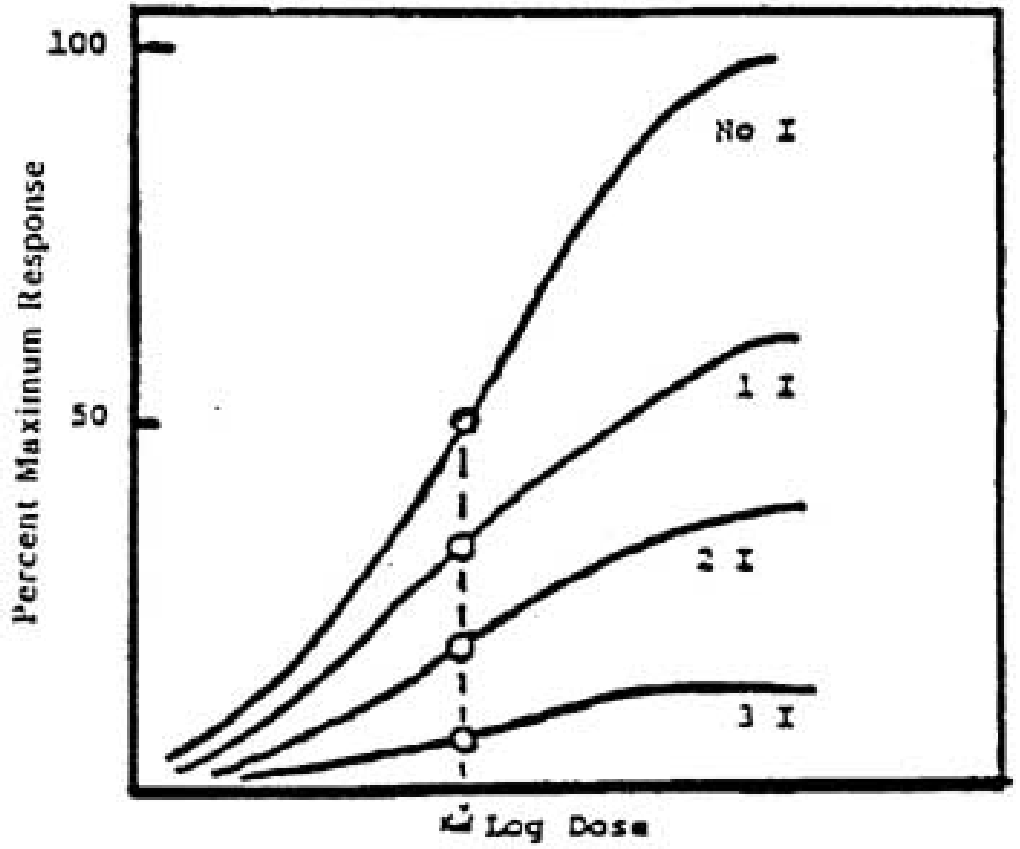
Competitive antagonism



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 Uptake of propranolol by isolated guinea-pig atria. J Pharmacol Exp Ther 55: 91-100.)

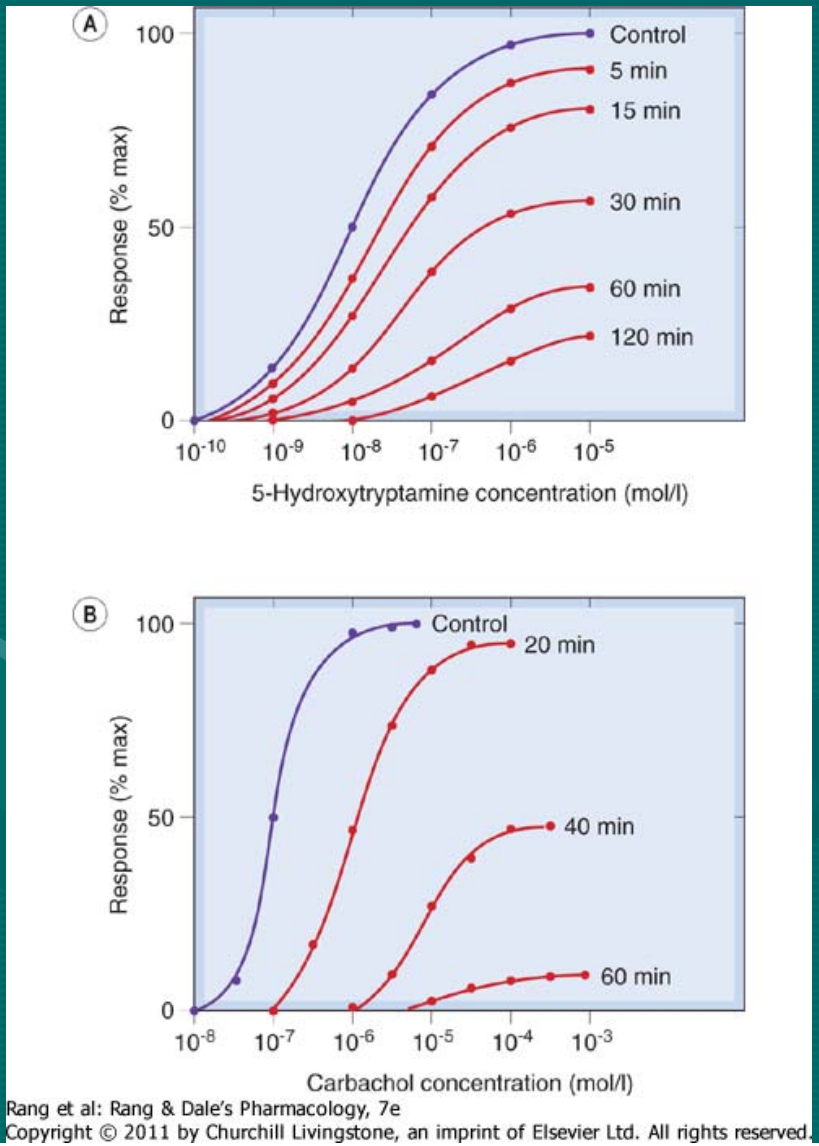
- **Non-Competitive or Non-Surmountable.** The antagonist changes the receptor to decrease the efficacy of the agonist or irreversibly blocks the agonist from combining with the receptor. The potency of a noncompetitive antagonist depends on its affinity its binding site and is independent of the dose of agonist and the relative affinity of the agonist. The effect is the same as eliminating a certain fraction of total receptor from the response. The maximum response to the agonist (power) is reduced, but potency remains the same.

Noncompetitive Antagonist



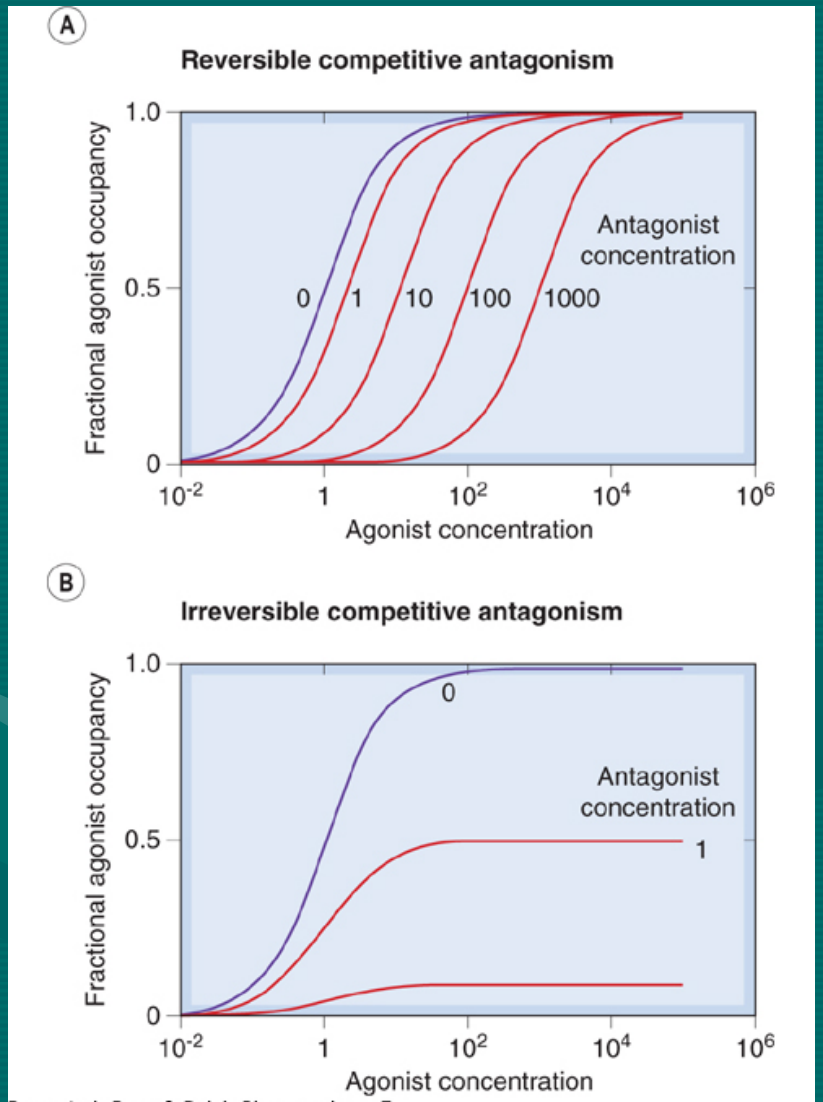
Log dose-response curves for a drug in the presence of increasing amounts of a non-competitive antagonist, I

Irreversible competitive antagonism



[**A**] Rat stomach smooth muscle responding to 5-hydroxytryptamine at various times after addition of methysergide (10^{-9} mol/l). [**B**] Rabbit stomach responding to carbachol at various times after addition of dibenamine (10^{-5} mol/l). ([**A**] After Frankhuijsen A L, Bonta I L 1974 Eur J Pharmacol 26: 220; [**B**] After Furchgott R F 1965 Adv Drug Res 3: 21.)

Comparison of reversible and irreversible antagonism



Hypothetical agonist concentration-occupancy curves in the presence of reversible [A] and irreversible [B] competitive antagonists. The concentrations are normalised with respect to the equilibrium constants, *K* (i.e. 1.0 corresponds to a concentration equal to *K* and results in 50% occupancy). Note that increasing the agonist concentration overcomes the effect of a reversible antagonist (i.e. the block is surmountable), so that the maximal response is unchanged, whereas the effect of an irreversible antagonist is unsurmountable and full agonist occupancy cannot be achieved.

Antagonism, Physiological

- Defined as the antagonism that results when two drugs produce opposite effects by interacting with two separate receptor systems; e.g., the effect of acetylcholine and norepinephrine on blood pressure when given simultaneously.

Antagonism, Chemical

- The antagonism of the effect of a drug by another agent as a result of chemical interaction; e.g., EDTA (a chelating agent) and lead.

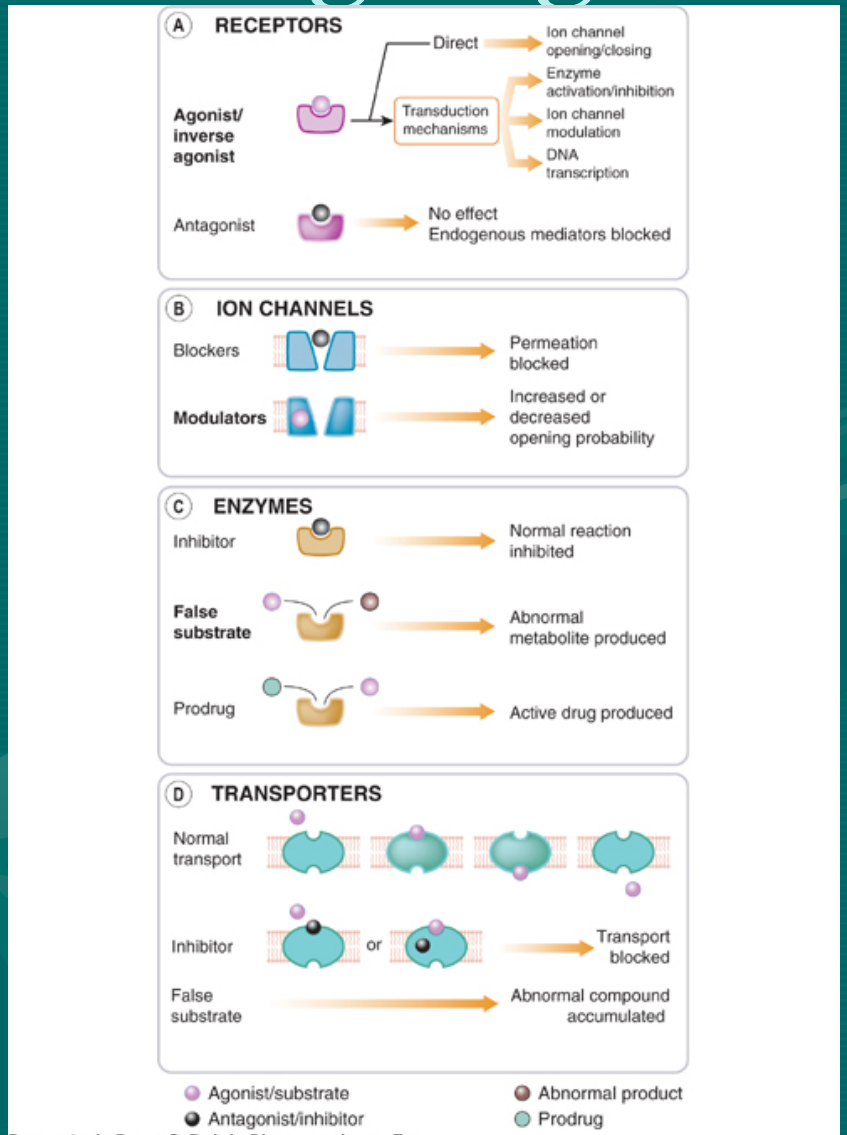
Additivity

- Administration of the dose of A and B simultaneously gives an effect equal to 20 units

Synergism

- A certain dose of Drug A alone produces an effect equal to 10 units. A certain dose of Drug B alone produces an effect equal to 10 units. Administration of the same doses of A and B simultaneously produces an effect equal to 50 units

Drug targets



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