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Slides pane showing a list of 7 slides. Slide 1 is the current slide. The list includes slide numbers and thumbnails of the slide content.

Main slide area with a red-to-yellow gradient background. The text reads:

PHARMACODYNAMICS

BY

DR. JAVAID

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Receptor: A molecule to which a drug binds to bring about a change in function of the biologic system.

Receptor site Specific region of the receptor molecule to which the drug binds.

Inert binding molecule or site: A molecule or a site to which a drug may bind without changing any function.

Effector: Component of a system that accomplishes the biologic effect after the receptor is activated by an agonist, often a channel or enzyme molecule.

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- 1 PHARMACODYNAMICS BY DR. JAVAJD
- 2 Receptor: A molecule with a deep groove to bring about a change in function of the biological system. Receptor sites: Specific region of a macromolecule. In this region, the drug binds. Small binding molecules or drugs. A molecule or a drug with a deep groove fits without changing its function. Characteristic: Compensatory response. In response to a change in the level of a receptor, a feedback system (homeostatic) restores to a normal or average value.
- 3 Receptors are the specific molecules in the biological system which bind drugs to produce a response in the cells of the system.
 - Receptors must be selective in their ligand-binding characteristics.
 - Receptor molecules are available in the cell & drug pressure increases and the functional response.
 - Many receptors have been purified, chemically characterized, and cloned. Most are proteins, a few are other macromolecules.
- 4 such as DNA.
 - The receptor is broken as conformation after drug binds. It is specific and depend on the receptor molecule itself.
 - Receptors high and sensitive only to the drug molecule. The response is high.
 - The rate of change of the functional response depends on the rate of drug-receptor binding.
 - "Tight" receptors: Specific conformation. Specific and irreversible binding. They are prone to be used targets for drug development.
- 5 Receptor-mediated drug action.
 - Receptor proteins
 - Structural proteins
 - The drug-receptor complex activates a regulatory protein which in turn causes a change in the functional response.
 - Examples: The case of receptors-released effects of many of the most used, marketed agents.
- 6 Other classes of proteins that have been identified include:
 - Enzymes, which release and activate an enzyme which produces the response.
 - G-proteins, which activate a G-protein which activates a regulatory protein which produces the response.
 - Second messengers (cyclic AMP, cAMP, cGMP, inositol triphosphate, diacylglycerol, etc.).
 - Intracellular proteins (kinases, phosphatases, etc.).
 - Receptors for neurotransmitters, hormones, and growth factors.
- 7 Receptors for many drugs have been identified and characterized.

RECEPTORS are the specific molecules in a biologic system with which drugs interact to produce changes in the function of the system.

- Receptors must be selective in their ligand-binding characteristics.
- Receptors must also be modifiable when they bind a drug molecule (so as to bring about the functional change).
- Many receptors have been identified, purified, chemically characterized, and cloned. Most are proteins; a few are other macromolecules

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Slides Outline

1 PHARMACODYNAMICS BY DR. JAVAI

2 Receptor: A molecule with a deep groove to bring about a change in function of the biological system. Specific region of the receptor molecule is called the binding site. Small binding molecules or drugs, a molecule or a drug with a deep groove without changing its function.

3 Receptors are the specific molecules in biological system which changes its function to produce a response in the cells of the system.

4 such as DNA.

5 Receptor proteins are the proteins that bind to a drug molecule and cause a change in the function of the cell.

6 Other classes of proteins that have been identified include enzymes, which modify the drug molecule, and transport proteins, which move the drug molecule across the cell membrane.

7 Receptor proteins are the proteins that bind to a drug molecule and cause a change in the function of the cell.

such as DNA.

➤ The **receptor site** (also known as **recognition site**) for a drug is the specific binding region of the receptor macromolecule and has a relatively high and selective affinity for the drug molecule. The interaction of a drug with its receptor is the fundamental event that initiates the action of the drug and many drugs are classified on the basis of their primary receptor affinity.

"orphan" receptors, so-called because their ligands are presently unknown; these may prove to be useful targets for future drug

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Slides Outline

1 PHARMACODYNAMICS BY DR. JAVAI

2 Receptor: A molecule with a deep hole to bring about a change in function of the biological system. Pharmacophore: Specific region of the receptor molecule that binds the drug. Small binding molecules or ligands. A molecule or a drug with a deep hole fits into the receptor without changing its function. Definition: Ligands bind to receptors and bind to receptors to produce a biological response.

3 Receptors are the specific molecules in the biological system which bind to ligands to produce a response in the body of the system. Receptors must be selective to their ligand binding characteristics. Receptor molecules are available on the cell's surface and are embedded in the lipid bilayer. Many receptors have been classified into different categories based on their structure, function and the mechanism of action.

4 Such as GPCR. The receptor is known as a G-protein coupled receptor (GPCR). It is a specific protein that binds to the receptor molecule and activates the receptor. The receptor is a transmembrane protein that spans the lipid bilayer. The receptor is a protein that is embedded in the lipid bilayer. The receptor is a protein that is embedded in the lipid bilayer. The receptor is a protein that is embedded in the lipid bilayer.

5 Receptor classification. Regulatory proteins. Enzymes. Structural proteins. The best characterized drug receptors are regulatory proteins which mediate the actions of endogenous chemical signals such as neurotransmitters, autacoids, and hormones. The class of receptors which mediate the actions of many of the most useful therapeutic agents.

6 Other classes of proteins that have been identified include ion channels, which regulate the flow of ions across the cell membrane. Some receptors are involved in the regulation of gene expression. Some receptors are involved in the regulation of cell growth and differentiation. Some receptors are involved in the regulation of cell death.

7 Receptors for many drugs are located on the cell surface. The receptors are located on the cell surface. The receptors are located on the cell surface. The receptors are located on the cell surface. The receptors are located on the cell surface.

Receptors may be

- Regulatory proteins
- Enzymes
- Transport proteins
- Structural proteins

■ The best-characterized drug receptors are **regulatory proteins which 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.

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Slides Outline

7 Receptors for ions shape is called and channels is called

8 Effectors: Component of a system that accomplishes the biologic effect after the receptor is activated by an agonist; often a channel or enzyme molecule.

9 Agonist: A drug that binds to a receptor and causes a response. It is a molecule that binds to a receptor and causes a response.

10 Second messenger: A signal that carries the effect of a hormone or neurotransmitter to a different receptor and causes a response.

11 Receptor: A protein that binds to a drug and causes a response.

12 Agonist: A drug that binds to a receptor and causes a response.

13 A full agonist binds with the highest affinity to the receptor and causes the maximum response.

Effectors: Component of a system that accomplishes the biologic effect after the receptor is activated by an agonist; often a channel or enzyme molecule. Effectors are molecules that translate the drug-receptor interaction into a change in cellular activity. The best examples of effectors are enzymes such as adenyl cyclase. Some receptors are also effectors in that a single molecule may incorporate both the drug-binding site & the effector mechanism eg a tyrosine kinase effector is part of the insulin receptor molecule & a Na-K channel is the effector part of the

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7 Receptor for ions shapes called ion channels in cell membrane. Changes in the channel reduce the flow of ions through the cell membrane. Transmitter release is dependent on receptor activity. Receptor activity is dependent on the binding of neurotransmitter.

8 Receptor: Component of membrane that binds neurotransmitter. Receptor activity is dependent on the binding of neurotransmitter. The binding of neurotransmitter to the receptor is reversible. The binding of neurotransmitter to the receptor is reversible. The binding of neurotransmitter to the receptor is reversible. The binding of neurotransmitter to the receptor is reversible.

9 Receptor: Ion channel. Agonist: A drug that activates its receptor upon binding. Antagonist: A drug that inhibits its receptor upon binding. Pharmacologic antagonist: A drug that binds without activating its receptor and thereby prevents activation by an agonist. Competitive antagonist: A pharmacologic antagonist that can be overcome by increasing the concentration of agonist. Irreversible antagonist: A pharmacologic antagonist that binds to the receptor and prevents activation by an agonist.

10 Pharmacologic antagonist: A drug that binds to a receptor and prevents activation by an agonist. Competitive antagonist: A pharmacologic antagonist that can be overcome by increasing the concentration of agonist. Irreversible antagonist: A pharmacologic antagonist that binds to the receptor and prevents activation by an agonist.

11 Receptor: Ion channel. Agonist: A drug that activates its receptor upon binding. Antagonist: A drug that inhibits its receptor upon binding. Pharmacologic antagonist: A drug that binds without activating its receptor and thereby prevents activation by an agonist. Competitive antagonist: A pharmacologic antagonist that can be overcome by increasing the concentration of agonist. Irreversible antagonist: A pharmacologic antagonist that binds to the receptor and prevents activation by an agonist.

12 Receptor: Ion channel. Agonist: A drug that activates its receptor upon binding. Antagonist: A drug that inhibits its receptor upon binding. Pharmacologic antagonist: A drug that binds without activating its receptor and thereby prevents activation by an agonist. Competitive antagonist: A pharmacologic antagonist that can be overcome by increasing the concentration of agonist. Irreversible antagonist: A pharmacologic antagonist that binds to the receptor and prevents activation by an agonist.

13 A full agonist binds with the highest affinity to the receptor and produces the maximum response. A partial agonist binds with a lower affinity to the receptor and produces a submaximal response. An antagonist binds with a low affinity to the receptor and prevents activation by an agonist.

nicotinic ACh receptor.

Agonist: A drug that activates its receptor upon binding. Has affinity & intrinsic activity.

Antagonist: A drug that inhibits its receptor upon binding. Has affinity but no intrinsic action

Pharmacologic antagonist: A drug that binds without activating its receptor and thereby prevents activation by an agonist.

Competitive antagonist: A pharmacologic antagonist that can be overcome by increasing the concentration of agonist.

Irreversible antagonist: A pharmacologic

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agonist concentration.

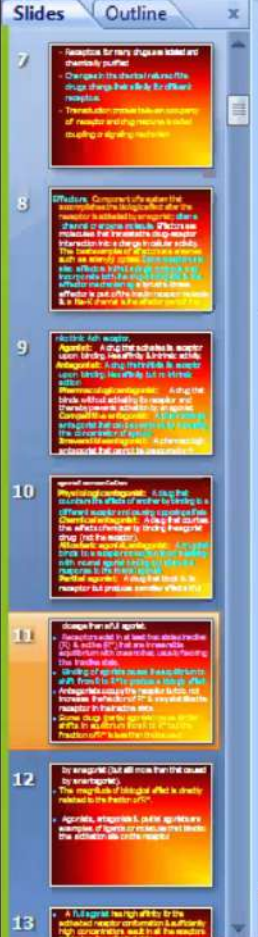
Physiologic antagonist: A drug that counters the effects of another by binding to a different receptor and causing opposing effects.

Chemical antagonist: A drug that counters the effects of another by binding the agonist drug (not the receptor).

Allosteric agonist, antagonist: A drug that binds to a receptor molecule without interfering with normal agonist binding but alters the response to the normal agonist.

Partial agonist: A drug that binds to its receptor but produces a smaller effect at full

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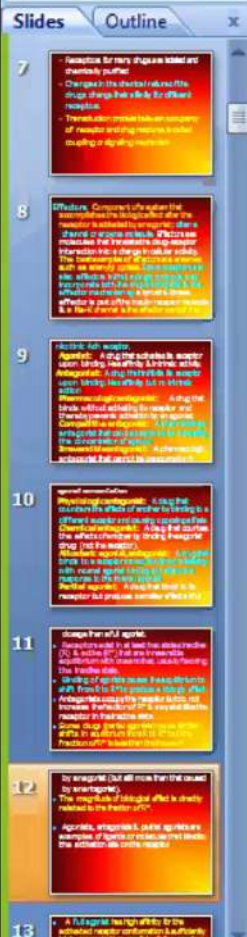


dosage than a full agonist.

- Receptors exist in at least two states inactive (R) & active (R*) that are in reversible equilibrium with one another, usually favoring the inactive state.
- Binding of agonists causes the equilibrium to shift from R to R* to produce a biologic effect.
- Antagonists occupy the receptor but do not increase the fraction of R* & may stabilize the receptor in the inactive state.
- Some drugs (partial agonists) cause similar shifts in equilibrium from R to R* but the fraction of R* is less than that caused

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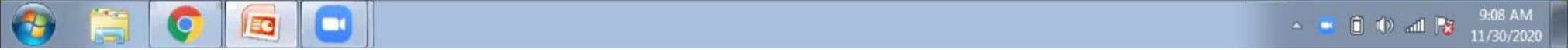


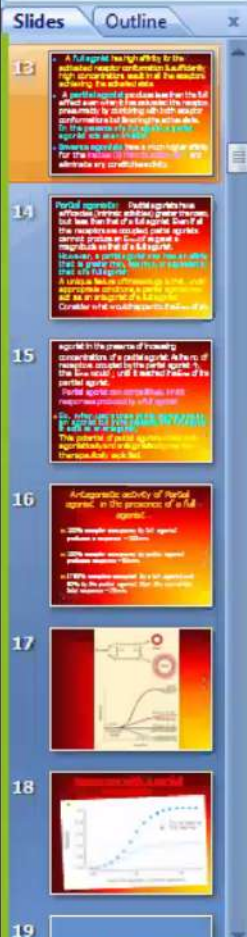


by an agonist (but still more than that caused by an antagonist).

- The magnitude of biological effect is directly related to the fraction of R^* .
- Agonists, antagonists & partial agonists are examples of ligands or molecules that bind to the activation site on the receptor.

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- A **full agonist** has high affinity for the activated receptor conformation & sufficiently high concentrations result in all the receptors achieving the activated state.
- A **partial agonist** produces less than the full effect even when it has saturated the receptors presumably by combining with both receptor conformations but favoring the active state. In the presence of a full agonist, a partial agonist acts as an inhibitor.
- **Inverse agonists** have a much higher affinity for the inactive (R) than for active (R*) and eliminate any constitutive activity.

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13 A full agonist has high affinity to the high and receptor concentration. As affinity increases, the maximum effect of the agonist increases. The affinity of a full agonist is high.

14 Partial agonists: Partial agonists have a lower efficacy (intrinsic activity) than full agonists. They bind to the same receptors as full agonists but produce a lower maximum effect. The efficacy of a partial agonist is lower than that of a full agonist.

15 Agonist in the presence of a partial agonist: In the presence of a partial agonist, the maximum effect of a full agonist is reduced. The partial agonist acts as a partial agonist and its effect is lower than that of a full agonist.

16 Antagonistic activity of partial agonist in the presence of a full agonist:

- 100% agonist response to full agonist
- 100% agonist response to partial agonist
- 100% agonist response to full agonist + partial agonist

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Partial agonists. Partial agonists have efficacies (intrinsic activities) greater than zero, but less than that of a full agonist. Even if all the receptors are occupied, partial agonists cannot produce an E_{max} of as great a magnitude as that of a full agonist. However, a partial agonist may have an affinity that is greater than, less than, or equivalent to that of a full agonist. A unique feature of these drugs is that, under appropriate conditions, a partial agonist may act as an antagonist of a full agonist. Consider what would happen to the E_{max} of an

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13 A full agonist has high affinity to the high number of receptors available. High concentrations reach 50% of the receptors binding. The affinity may be a product of the number of receptors and the full effect over time. It is considered the receptor placement by concentration of the receptor concentration. In the presence of a partial agonist, the full effect is not reached. The partial agonist has a higher affinity for the receptors than the full agonist. The full agonist is considered to be a high-affinity agonist.

14 Partial agonists: Partial agonists have a lower affinity for the receptors than full agonists. The receptors occupied by partial agonists are less than those of a full agonist. However, a partial agonist can have a higher affinity than a full agonist. A partial agonist can act as a full agonist if the concentration is high enough. Consider the following examples:

15 agonist in the presence of increasing concentrations of a partial agonist. As the no. of receptors occupied by the partial agonist increases, the full effect of the full agonist is inhibited. Partial agonist can act as a full agonist if the concentration is high enough. The partial agonist can act as a full agonist if the concentration is high enough. The partial agonist can act as a full agonist if the concentration is high enough.

16 Antagonistic activity of partial agonist in the presence of a full agonist:

- 100% agonist response to full agonist
- 100% agonist response to partial agonist
- 100% agonist response to full agonist + partial agonist

17

18

19

agonist in the presence of increasing concentrations of a partial agonist. As the no. of receptors occupied by the partial agonist ↑, the E_{max} would ↓ until it reached the E_{max} of the partial agonist.

Partial agonist can competitively inhibit responses produced by a full agonist.

- So, when used alone a partial agonist acts as an agonist but in the presence of a full agonist it acts as an antagonist.

This potential of partial agonists to act both agonistically and antagonistically may be therapeutically exploited.

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13 A full agonist has high affinity to the high concentration of receptors...
14 Partial agonists: Partial agonists have a lower affinity for the receptors...
15 Agonist in the presence of a weakly binding antagonist...
16 Antagonistic activity of partial agonist in the presence of a full agonist...
17
18
19

Antagonistic activity of Partial agonist in the presence of a full agonist

- 100% receptor occupancy by full agonist produces a response = 100mm.
- 100% receptor occupancy by partial agonist produces response = 50mm.
- If 50% receptors occupied by a full agonist and 50% by the partial agonist then the sum of the total response = 75mm.

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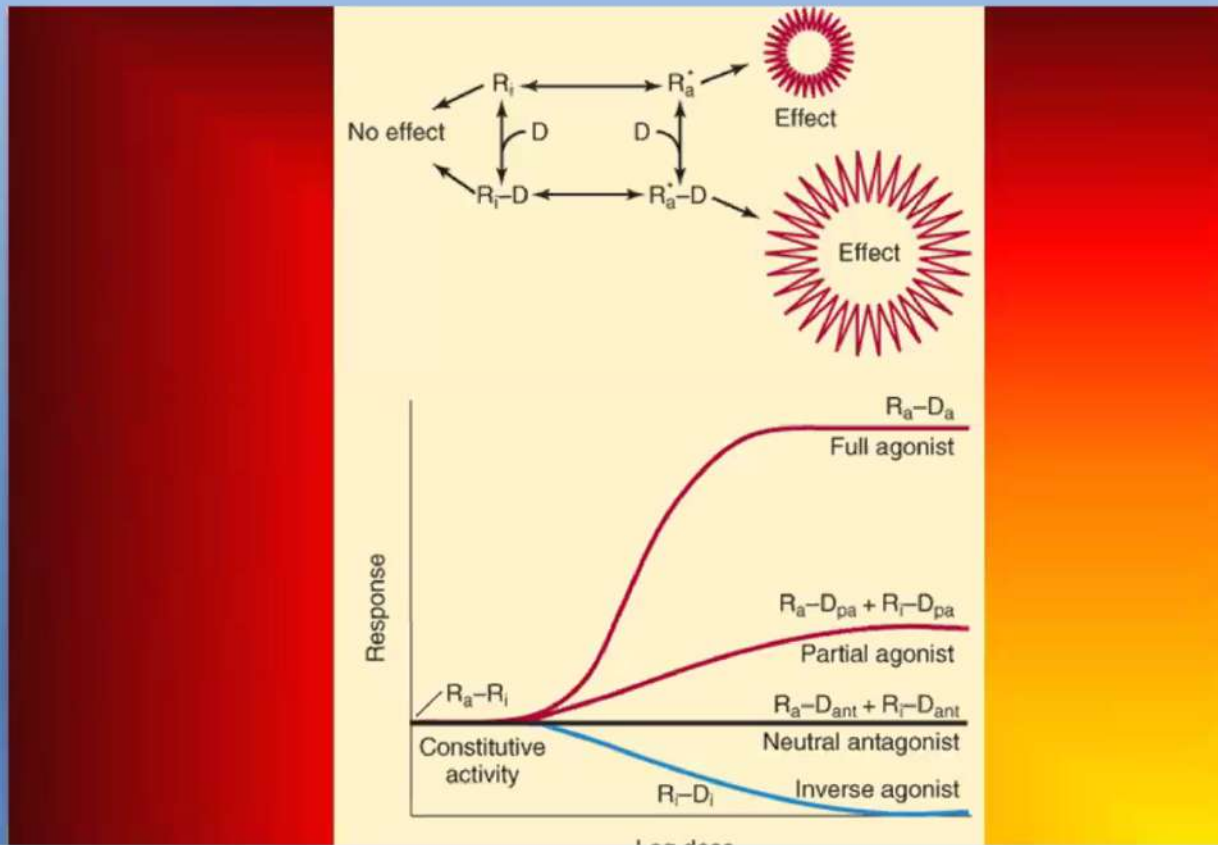
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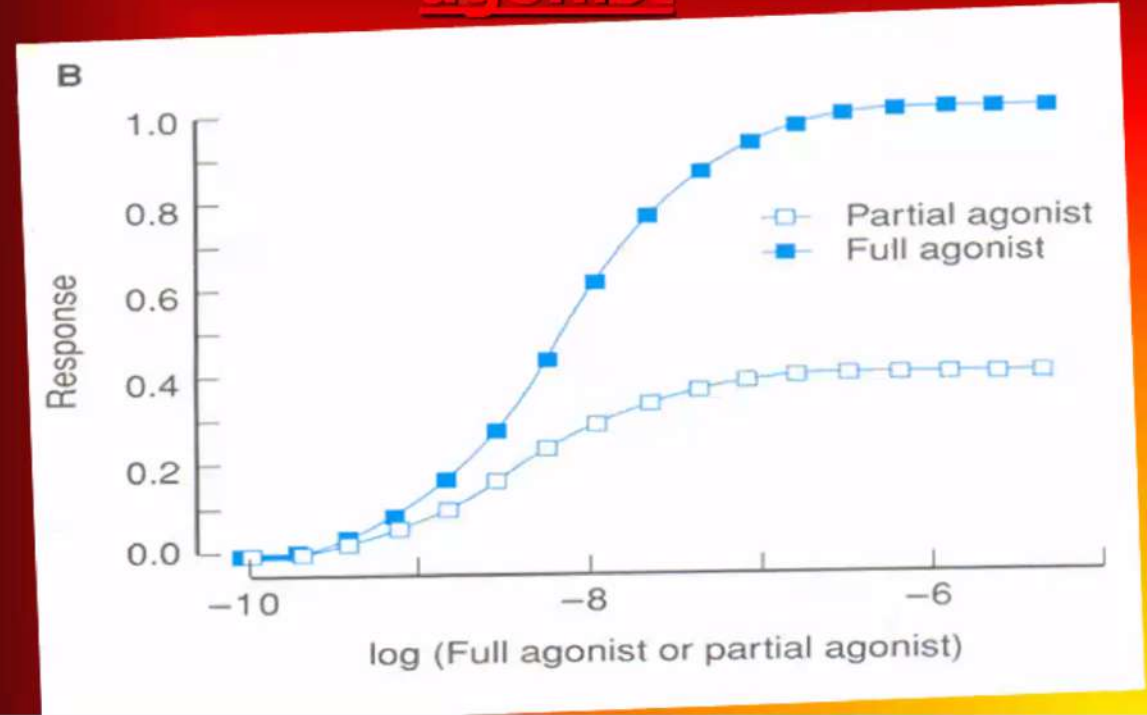
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- 13 A full agonist has high affinity to the receptor and high efficacy. It binds to the receptor and produces a high response. The maximum response is achieved when all the receptors are occupied. It is characterized by a high EC_{50} and a high E_{max} .
- 14 Partial agonists: Partial agonists have a lower affinity and/or lower efficacy than full agonists. They bind to the receptor and produce a lower response. The maximum response is lower than that of a full agonist. They are characterized by a lower EC_{50} and a lower E_{max} .
- 15 Agonist in the presence of a weakly binding antagonist: In the presence of a weakly binding antagonist, the response of a full agonist is reduced. The EC_{50} is shifted to the right, and the E_{max} is reduced. The response is characterized by a higher EC_{50} and a lower E_{max} .
- 16 Antagonistic activity of partial agonist in the presence of a full agonist: In the presence of a full agonist, the response of a partial agonist is reduced. The EC_{50} is shifted to the right, and the E_{max} is reduced. The response is characterized by a higher EC_{50} and a lower E_{max} .
- 17
- 18
- 19

Response with a partial agonist



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Slides Outline

19 Graded dose-response curve: A graph of increasing response to increasing drug conc. or dose.

20 Quantal dose-response curve: A graph of the fraction of a population that shows a specified response to progressively inc. doses.

21 3 aspects of drug receptor function derived discussion.

22 Concentration effect curves

23 Receptor binding of agonist & antagonist

24 SOME LONG DOSE RESPONSE CURVES

25

Graded dose-response curve: A graph of increasing response to increasing drug conc. or dose.

Quantal dose-response curve: A graph of the fraction of a population that shows a specified response at progressively inc. doses.

K_d : The concentration of drug that binds 50% of the receptors in the system.

Efficacy, maximal efficacy E_{max} : The maximum effect that can be achieved with a particular drug, regardless of dose.

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Slides Outline

19 Graded dose-response curve: A graph of increasing response to increasing drug conc or dose.

20 ED₅₀, TD₅₀, etc. In graded dose-response curves, the concentration or dose that causes 50% of the maximum effect or toxicity in quantal dose-response curves, the concentration or dose that causes a specified response in 50% of the population under study.

21 3 aspects of drug receptor function derived discussion.

22 Concentration effect curves

23 Receptor binding of agonist & antagonist

24 SOME LONG DOSE RESPONSE CURVES

25 SIGNIFICANCE OF RECEPTOR TRANSDUCTION

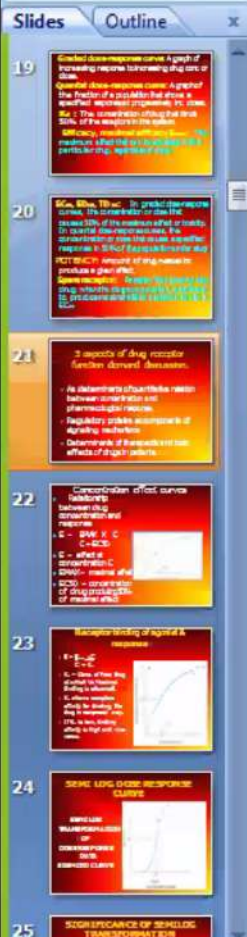
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EC₅₀, ED₅₀, TD₅₀: In graded dose-response curves, the concentration or dose that causes 50% of the maximum effect or toxicity. In quantal dose-response curves, the concentration or dose that causes a specified response in 50% of the population under study.

POTENCY: Amount of drug needed to produce a given effect.

Spare receptor: Receptor that does not bind drug when the drug concentration is sufficient to produce maximal effect; present when $K_d > EC_{50}$

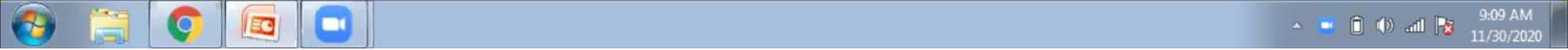
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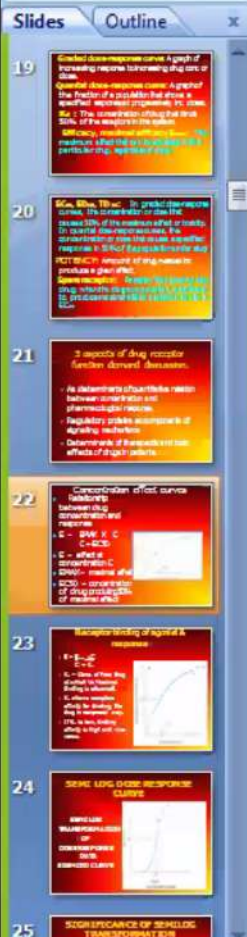


CONCENTRATION EFFECT CURVES

- Relationship between drug concentration and response
- $E = \frac{EMAX \times C}{C + EC50}$
- E = effect at concentration C
- EMAX = maximal effect
- EC50 = concentration of drug producing 50%

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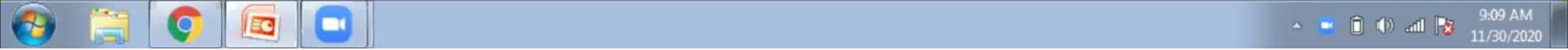




CONCENTRATION EFFECT CURVES

- Relationship between drug concentration and response
- $E = \frac{EMAX \times C}{C + EC50}$
- E = effect at concentration C
- EMAX = maximal effect
- EC50 = concentration of drug producing 50%

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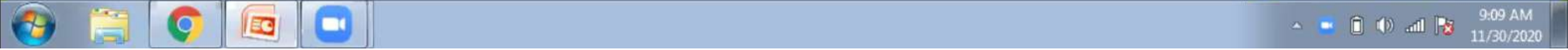


- 19 Graded dose-response curve: A graph of increasing response to increasing drug conc of drug.
- 20 Quantal dose-response curve: A graph of the fraction of a population that shows a specified response (response) to dose. The concentration at which 50% of the population shows the response is the ED50.
- 21 3 aspects of drug receptor function derived discussion.
- 22 Concentration effect curves relationship between drug concentration and response.
- 23 Receptor binding of agonist & response.
- 24 SOME LOG DOSE RESPONSE CURVES.
- 25 SOME RESPONSE OF RECEPTOR TRANSDUCTION.

Receptor binding of agonist & response

- $B = \frac{B_{max} \times C}{C + K_D}$
- $K_D =$ Conc. of Free drug at which $\frac{1}{2}$ Maximal binding is observed.
- K_D shows receptors affinity for binding the drug in reciprocal way.
- If K_D is low, binding affinity is high and vice versa.

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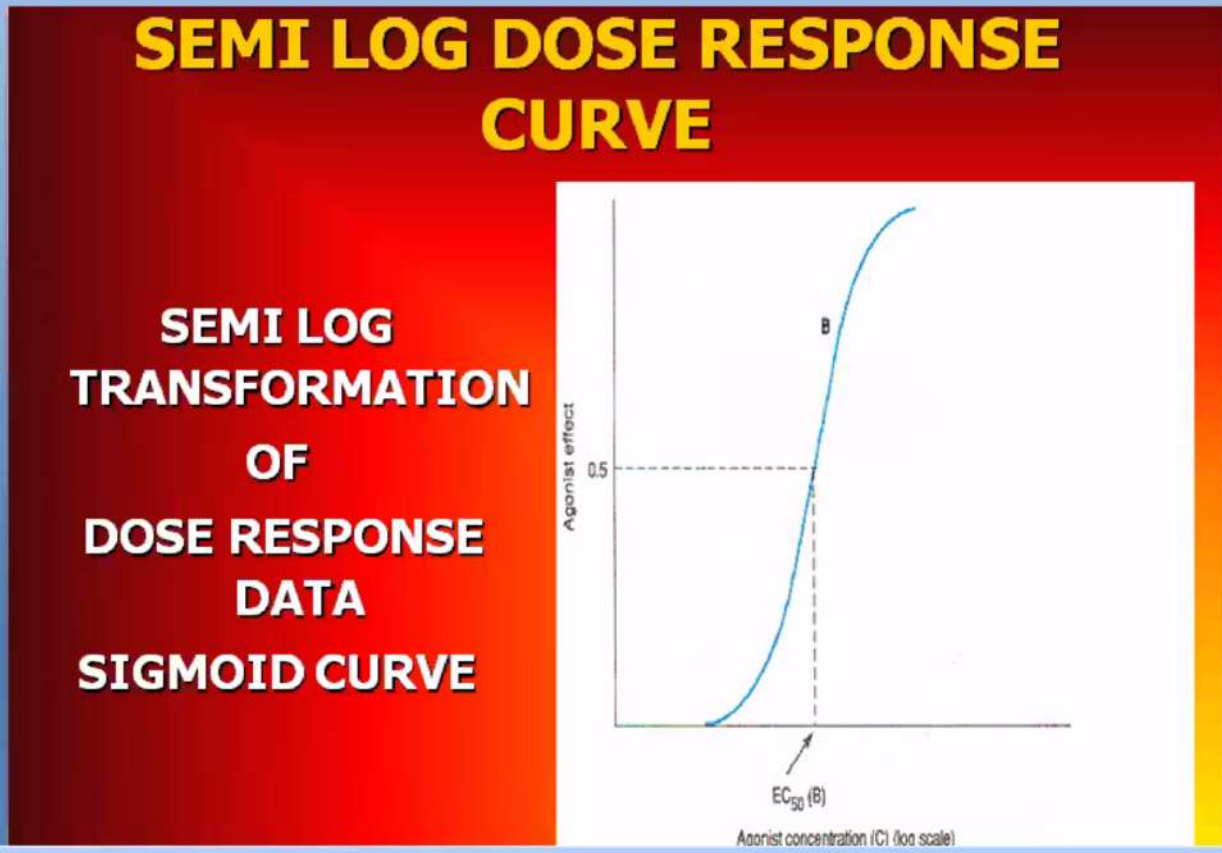
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- 19 Graded dose response curve: A graph of increasing response to increasing drug dose or concentration. Quantal dose response curve: A graph of the fraction of a population that shows a specified response (response to death, etc.). The concentration giving 50% of the response is the ED₅₀. Efficacy, maximal effect, is the maximum effect that can be achieved by a particular drug, regardless of dose.
- 20 ED₅₀, TD₅₀ etc. In graded dose response curves, the concentration of a drug that causes 50% of its maximum effect is usually its quantal dose response. It is a concentration that produces a 50% response in a particular population. ED₅₀ is the concentration of a drug that produces a 50% response in a particular population. TD₅₀ is the concentration of a drug that produces a 50% response in a particular population. The difference between ED₅₀ and TD₅₀ is the therapeutic index.
- 21 3 aspects of drug receptor function discussed:
 - As determinants of quantitative relationships between concentration and pharmacological response.
 - Regulatory protein involvement in drug-receptor interaction.
 - Determinants of pharmacological effects of drug actions.
- 22 Concentration effect curves:
 - Relationship between drug concentration and response.
 - $E = \frac{E_{max} \cdot C}{C + EC_{50}}$
 - E - effect
 - C - concentration
 - E_{max} - maximal effect
 - EC_{50} - concentration of drug producing 50% of maximal effect.
- 23 Receptor binding of agonist & response:
 - $E = \frac{E_{max} \cdot [D]}{K_d + [D]}$
 - E - Effect of the drug
 - E_{max} - Maximal effect
 - $[D]$ - Drug concentration
 - K_d - Dissociation constant
 - K_d is the concentration of drug that gives a half-maximal effect.
- 24 SEMI LOG DOSE RESPONSE CURVE:
 - MAXIMAL RESPONSE OF AN AGONIST IS THE SAME REGARDLESS OF THE DOSE RESPONSE CURVE.
- 25 SIGNIFICANCE OF SEMI LOG TRANSFORMATION



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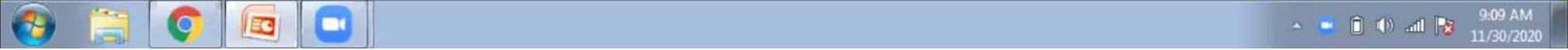


- 25 SIGNIFICANCE OF SEMILOG TRANSFORMATION
- 26 Receptor-effector coupling
- 27 SPARE RECEPTORS
- 28 In practice, bioassay is usually made by comparing the concentration for 50% of maximal effect (EC₅₀) with the one for 50% of maximal effect (EC₅₀)
- 29 They graph called the sigmoidal interaction, have maximal response, shifted to the left or right by the addition of another agonist. The maximal response is the same, but the EC₅₀ is shifted to the left or right.
- 30 The relationship of fractional level of receptor occupancy, the number of receptors occupied, to the concentration of agonist is a hyperbolic curve. The relationship of the effect to the concentration of agonist is a sigmoidal curve.
- 31 The graph is sigmoidal and with two receptors and four effectors, the number of effectors occupied is the same as the number of receptors occupied.

SIGNIFICANCE OF SEMILOG TRANSFORMATION

- Transforms hyperbolic curve into sigmoid curve
- Mid portion is linear
- Expands scale of concentration axis where at low concentrations, effect is changing rapidly
- Compresses scale at high conc. where effect is changing slowly.

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Slides Outline

25 SIGNIFICANCE OF SIGNAL TRANSDUCTION

26 Receptor-Effector Coupling

27 SPARE RECEPTORS

28 Intrinsic transduction is usually measured by comparing the concentration of the agonist (EC50) with the concentration of the receptor (EC50).

29 They graph called the agonist-receptor interaction, have maximal response, called the maximum effect (Emax) or the maximum response (Emax).

30 Transduction of biochemical signal of receptor occurs. The activation of the receptor causes the activation of the effector. The effector then produces the response.

31 Imagine a receptor with two receptors and four effectors. Assume that the number of effectors is limited to two. Assume that the number of effectors is limited to two.

Receptor-Effector Coupling

- Receptor occupancy by agonist results in a conformational change
- Transduction process between occupancy of receptor and drug response is termed coupling
- The relative efficiency of occupancy response coupling is determined by the initial conformational change in the receptor
- Effect of full agonist is due to more efficiently coupled to receptor occupancy [vs. partial agonist]
- Coupling efficiency is also determined by biochemical events, transducing receptor occupancy into cellular response.

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25 SIGNIFICANCE OF SIGNAL TRANSDUCTION

26 Receptor-effector coupling

27 SPARE RECEPTORS

28 In practice, bioassay is usually done by comparing the concentration for 50% of maximal effect (EC₅₀) with the one for 50% of maximal effect (ED₅₀)

29 They graph the agonist-receptor interaction, i.e., maximal response, about the addition of agonist. The resulting curve is sigmoidal. The maximum response is called the maximal effect (E_{max}). The concentration of agonist that produces 50% of the maximal response is called the EC₅₀.

30 The presence of spare receptors allows the system to respond to a lower concentration of agonist than would be expected from the number of receptors present.

31 Imagine a receptor with two binding sites and four effectors. Assume that the number of effectors is limited to two. Assume that the number of effectors is limited to two.

SPARE RECEPTORS

Receptors that do not bind drug when drug conc. is sufficient to produce max. effect or when the maximal response can be elicited by an agonist at a conc. that does not result in occupancy of full complement of available receptors eg max inotropic response of heart muscle after 90% occupancy of beta adrenoceptors by irreversible antagonist. Spare receptors are said to exist if the maximal drug response (E_{max}) is obtained at less than

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25 SIGNIFICANCE OF SIGNAL TRANSDUCTION

26 Receptor-effector coupling

27 SPARE RECEPTORS

28 In practice, the determination is usually made by comparing the concentration for 50% of maximal effect (EC_{50}) with the conc. for 50% of maximal binding (K_d).

29 They graph called the spare-receptor interaction. In this graph, the maximal response is obtained by addition of infinite drug concentration. The number of receptors is finite. The number of receptors is larger than the number of receptors that are needed to produce the maximal response.

30 The presence of functional reserve of receptor allows the system to respond to a larger dose of drug. The system is able to respond to a larger dose of drug because the number of receptors is larger than the number of receptors that are needed to produce the maximal response.

31 Temporal spareness is a property of receptors and effector systems. It is the ability of a system to respond to a larger dose of drug because the number of receptors is larger than the number of receptors that are needed to produce the maximal response.

In practice, the determination is usually made by comparing the concentration for 50% of maximal effect (EC_{50}) with the conc. for 50% of maximal binding (K_d).

If the EC_{50} is less than the K_d , spare receptors are said to exist.

This might result from 1 of 2 mechanisms.

- First, the duration of the activation of the effector may be much greater than the duration of the drug-receptor interaction (**temporal spareness**). eg β -receptor activation by an agonist promotes binding of guanosine triphosphate (GTP) to a trimeric G protein, an

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25 SIGNIFICANCE OF SIGNAL-TRANSDUCTION

26 Receptor-effector coupling

27 SPARE RECEPTORS

28 In practice, bioassay systems usually measure the concentration of the effector molecule (rather than the concentration of the receptor) to determine the effect of a drug.

29 They are called spare receptors because the maximal response is achieved by occupying only a fraction of the total number of receptors.

30 The presence of spare receptors allows the system to respond to a lower concentration of the drug than would be required if all receptors were needed to produce a maximal response.

31 Imagine a receptor with two binding sites and four effectors. Assume that the number of effectors is equal to the number of receptors.

4 3 2 1 0 1 2 3 4

3
2
1
0
1
2
3

may greatly outlast the agonist-receptor interaction. Here, maximal response is elicited by activation of relatively few receptors because the response initiated by an individual ligand-receptor-binding event persists longer than the binding event itself.

➤ Second the actual number of receptors may exceed the number of effector molecules available (**spareness in number**) ie receptors may be simply *spare in number relative to the* total number of downstream signaling mediators present in the cell, so that a maximal response occurs without occupancy

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25 SIGNIFICANCE OF SPARE RECEPTORS

26 Receptor-Receptor Coupling

27 SPARE RECEPTORS

28 In practice, bioassay is usually made by comparing the concentration for 50% of maximal effect (EC₅₀) with the EC₅₀ of maximal effect (EC₅₀).

29 They graph called the spare-receptor interaction. In this graph, the maximal response is shifted to the left of the maximal response. This is because the number of spare receptors is large.

30 The presence of spare receptors allows for a greater degree of reserve. This is because the number of spare receptors is large.

31 The graph is a graph of the response and four different levels of response. The number of receptors is constant. The number of spare receptors is large.

3 2 1 0 1 2 3 4

receptor reserve, the sensitivity of a cell or tissue to a particular concentration of agonist depends not only on the affinity of the receptor for binding the agonist (characterized by the K_d) but also on the degree of spareness—the total number of receptors present compared with the number actually needed to elicit a maximal biologic response.

SIGNIFICANCE: The presence of spare receptors ↑ sensitivity to the agonist because the likelihood of a drug–receptor interaction ↑ in proportion to the number of receptors available

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31 Imagine a responding cell with four receptors and four effectors. Here the number of effectors does not limit the maximal response & receptors are not spare in number. So an agonist present at a concentration equal to the K_d will occupy 50% of the receptors & half of the effectors will be activated, producing a half-maximal response (ie, two receptors stimulate two effectors).

32 As a result, a multi-receptorization of agonist is sufficient to occupy 50% of the receptors & half of the effectors will be activated, producing a half-maximal response (ie, two receptors stimulate two effectors).

33 4 receptors
4 effectors
2 bound out of 4 agonist conc. = K_d
50% receptors bound
50% effectors activated

34 40 receptors
4 effectors
2 bound out of 4 agonist conc. = K_d
5% receptors bound
50% effectors activated
Increase sensitivity of a drug binding
They need to fit the efficacy of receptor-effector interaction.

35 DIFFERENCE BETWEEN EC₅₀ AND EC₅₀
EC₅₀ is the conc of drug that produce 50% of maximal response.
EC₅₀ represents the conc of binding to which half maximal efficacy is achieved.
In a system with spare receptors, EC₅₀ and EC₅₀ are identical.
If there are no spare receptors, EC₅₀ is lower than EC₅₀.

36 DIFFERENTIAL EFFECTS OF SPARE RECEPTORS
- maximal response is not affected by spare receptors
- potency is increased by spare receptors
- EC₅₀ is decreased by spare receptors
- EC₅₀ is decreased by spare receptors

37 DRUG ANTAGONISM

Imagine a responding cell with four receptors and four effectors. Here the number of effectors does not limit the maximal response & receptors are not spare in number. So an agonist present at a concentration equal to the K_d will occupy 50% of the receptors & half of the effectors will be activated, producing a half-maximal response (ie, two receptors stimulate two effectors).

Now imagine that the number of receptors ↑ tenfold to 40 receptors but that the total number of effectors remains constant. Most of the receptors are now spare in number.

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32 AS a result, a much lower concentration of agonist is sufficient to occupy 2 of the 40 receptors (5% of the receptors), and this same low concentration of agonist is able to elicit a half-maximal response i.e. EC_{50} (two of four effectors activated).

- Thus, it is possible to change the sensitivity of tissues with spare receptors by changing receptor number.

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80%

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31 Imagine a receptor with four receptors and four effectors. Assume number of effectors bound to the receptor is proportional to the number of receptors bound to the receptor. Do an agonist concentration of 100 nM. For all concentrations of the agonist, the number of receptors bound to the agonist is proportional to the number of receptors. How many effectors are bound to the receptor at this concentration?

32 As a result, a 100 nM concentration of agonist, 100 nM concentration of agonist will bind to four receptors (four receptors are bound to the agonist). Think, if a receptor has four receptors, how many effectors are bound to the receptor at this concentration?

33 A: 4 receptors
4 effectors
2 bound out of 4
agonist conc. = K_d
50% receptors bound produce EC_{50}

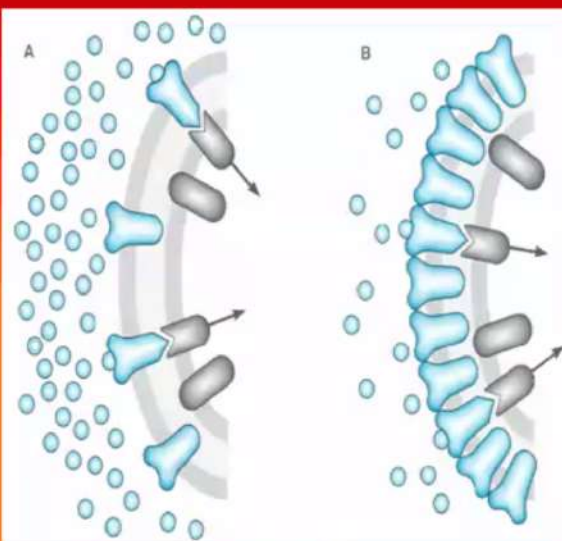
34 D: 40 receptors
4 effectors
2 bound out of 4
50% receptors bound produce EC_{50}
Increase sensitivity of a receptor.
This results in the efficacy of receptor.

35 DIFFERENCE BETWEEN EC_{50} AND IC_{50}
 EC_{50} is the concentration that produces 50% of maximal response.
 IC_{50} represents the concentration of the drug that inhibits 50% of the maximal response.
In a system with spare receptors, EC_{50} and IC_{50} are different.
If there are spare receptors, EC_{50} is lower than IC_{50} .

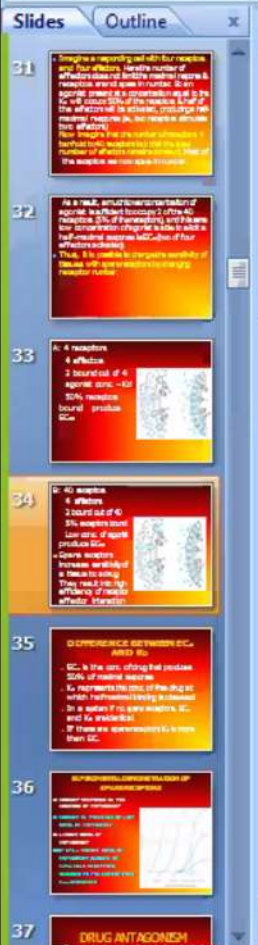
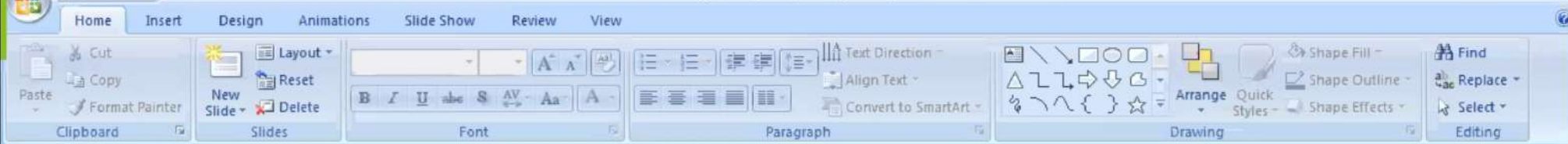
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37 DRUG ANTAGONISM

A: 4 receptors
4 effectors
2 bound out of 4
agonist conc. = K_d
50% receptors bound produce EC_{50}

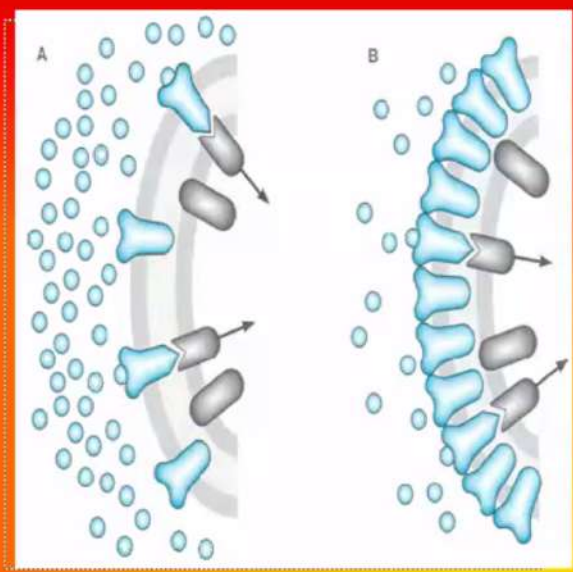


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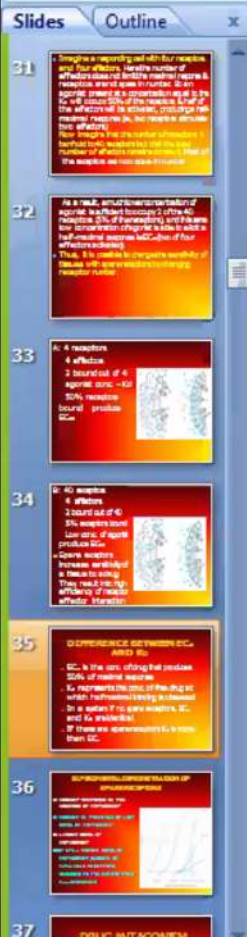
D. 40 receptors
4 effectors
2 bound out of 40
5% receptors bound
Low conc. of agonist
produce EC₅₀

- Spare receptors increase sensitivity of a tissue to a drug. They result into high efficiency of receptor



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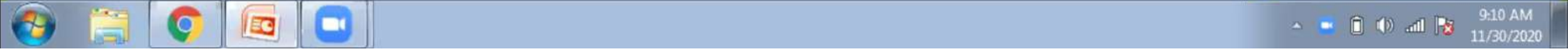




DIFFERENCE BETWEEN EC_{50} AND K_D

- EC_{50} is the conc. of drug that produces 50% of maximal response
- K_D represents the conc. of free drug at which half maximal binding is observed
- In a system if no spare receptors, EC_{50} and K_D are identical.
- If there are spare receptors K_D is more than EC_{50}

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- 31. Imagine a receptor with four receptors and four effectors. Assume the number of effectors is equal to the number of receptors and that the number of receptors is equal to the number of effectors. For all agonists, the number of receptors is equal to the number of effectors. The receptor is not saturated.
- 32. As a result, an agonist concentration of 100 nM produces 50% of the maximal effect. If the number of receptors is reduced to 200, the number of effectors is also reduced to 200. The number of receptors is equal to the number of effectors. The receptor is not saturated.
- 33. A. 4 receptors
2 bound out of 4 agonist conc. = 50% bound out of 4 receptors bound out of 4 effectors
- 34. D. 40 receptors
2 bound out of 40 agonist conc. = 5% bound out of 40 receptors bound out of 40 effectors
- 35. DIFFERENCE BETWEEN EC₅₀ AND EC₅₀
EC₅₀ is the conc. of drug that produce 50% of maximal response.
EC₅₀ represents the conc. of drug that binds to 50% of the receptors.
In a system with spare receptors, EC₅₀ and EC₅₀ are different.
If there are spare receptors, EC₅₀ is less than EC₅₀.
- 36. DRUG ANTAGONISM
- 37. DRUG ANTAGONISM

EXPERIMENTAL DEMONSTRATION OF SPARE RECEPTORS

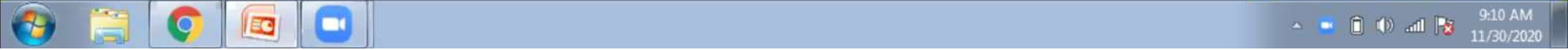
A: AGONIST RESPONSE IN THE ABSENCE OF ANTAGONIST

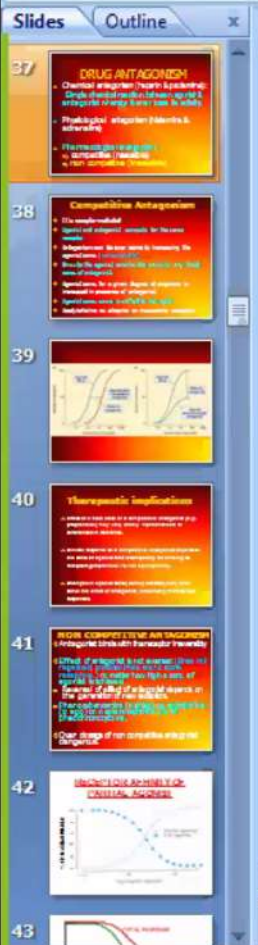
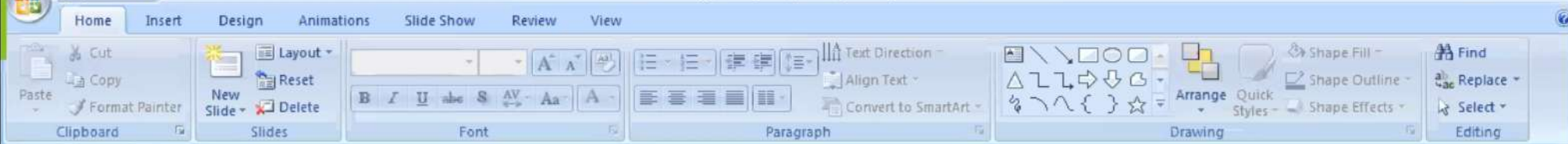
B: AGONIST IN PRESENCE OF LOW CONC. OF ANTAGONIST

C: LARGER CONC. OF ANTAGONIST

D&E: STILL HIGHER CONC. OF ANTAGONIST, NUMBER OF AVAILABLE RECEPTORS REDUCED TO THE EXTENT THAT E_{MAX} DIMINISHED

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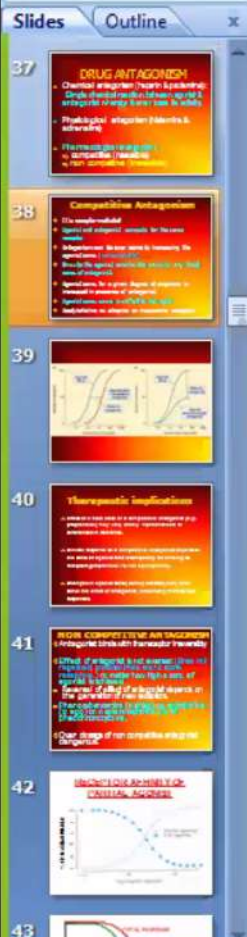


DRUG ANTAGONISM

- ❖ Chemical antagonism (heparin & protamine):
Simple chemical reaction between agonist & antagonist whereby former loses its activity.
- ❖ Physiological antagonism (histamine & adrenaline)
- ❖ Pharmacological antagonism:
 - a). competitive (reversible)
 - b). non competitive (irreversible)

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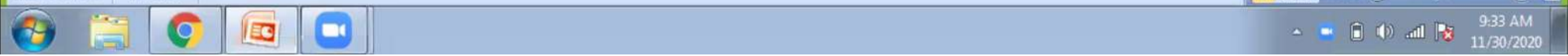




Competitive Antagonism

- ◆ It is receptor mediated
- ◆ Agonist and antagonist compete for the same receptor
- ◆ Antagonism can be over come by increasing the agonist conc. (surmountable)
- ◆ E_{max} for the agonist remains the same for any fixed conc. of antagonist.
- ◆ Agonist conc. for a given degree of response is increased in presence of antagonist.
- ◆ Agonist conc. curve is shifted to the right.
- ◆ Acetylcholine vs. atropine on muscarinic receptors

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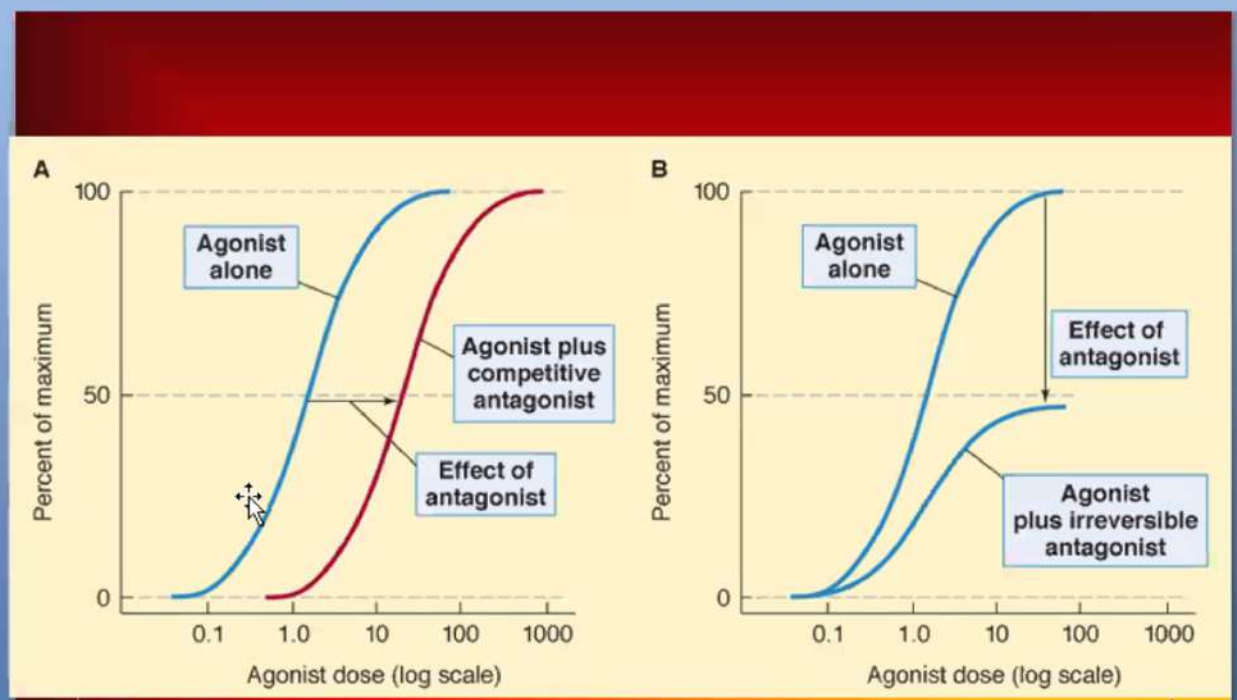
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- 36
- 37 DRUG ANTAGONISM
 - Chemical antagonism (Direct Antagonism)
 - Physiological antagonism (Indirect Antagonism)
 - Pharmacological antagonism (Competitive Antagonism)
 - Pharmacological antagonism (Non-competitive Antagonism)
 - Pharmacological antagonism (Irreversible Antagonism)
- 38 Competitive Antagonism
 - It is non-covalent
 - Agonist and antagonist compete for the same receptor
 - Antagonism can be overcome by increasing the concentration of agonist
 - Non-competitive antagonism is not overcome by increasing the concentration of agonist
 - Antagonism is reversible
 - Antagonism is reversible
- 39
- 40 Therapeutic Implications
 - Antagonism can be used to reduce the side effects of a drug
 - Antagonism can be used to reduce the toxicity of a drug
 - Antagonism can be used to reduce the duration of action of a drug
 - Antagonism can be used to reduce the onset of action of a drug
- 41
- 42



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40 Therapeutic implications

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Therapeutic implications

- ✦ Effect of a fixed dose of a competitive antagonist (e.g. propranolol) may vary widely in patients due to differences in clearance.
- ✦ Clinical response to a competitive antagonist depends on the conc. of agonist that is competing for binding to receptors (propranolol vs. nor epinephrine).
- ✦ Changes in agonist conc.(during exercise) may overcome the effect of antagonist, influencing therapeutic

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NON COMPETITIVE ANTAGONISM

- ☀ Antagonist binds with the receptor irreversibly
- ☀ Effect of antagonist is not reversed (E_{max} not regained, provided there are no spare receptors.) no matter how high a conc. of agonist is achieved.
- Reversal of effect of antagonist depends on the generation of new receptors.
- Phenoxybenzamine (α antag) vs. epinephrine (α ago) on α adrenoceptors in pts of pheochromocytoma.
- ☀ Over dosage of non competitive antagonist dangerous

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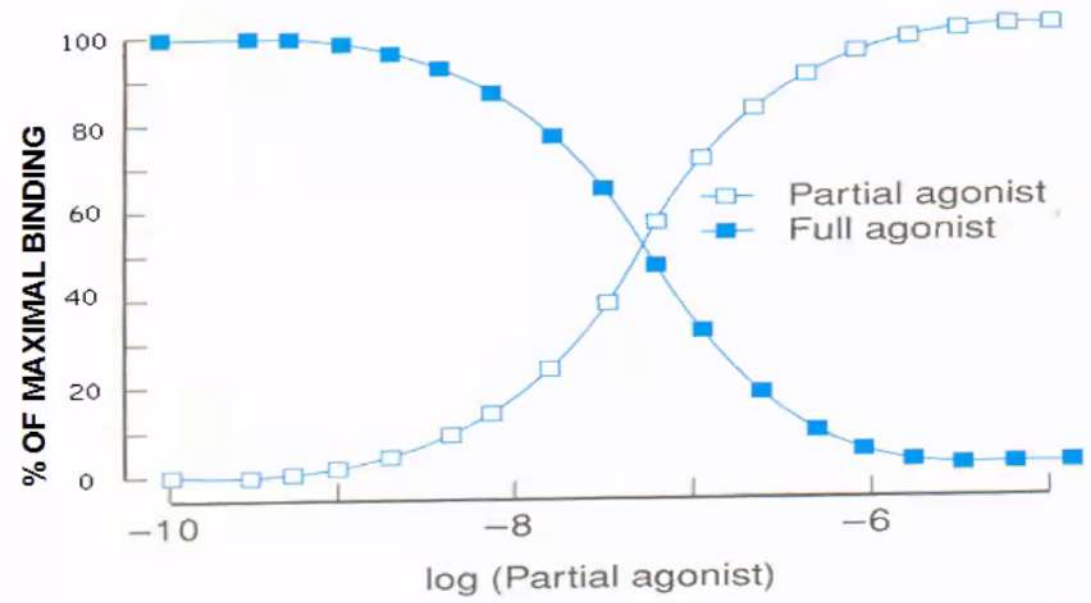
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RECEPTOR AFFINITY OF PARTIAL AGONIST



Slides Outline

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40 Therapeutic Implications

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44 RELATION BETWEEN DRUG DOSE AND CLINICAL RESPONSE

45 POTENCY AND MAXIMAL EFFICACY

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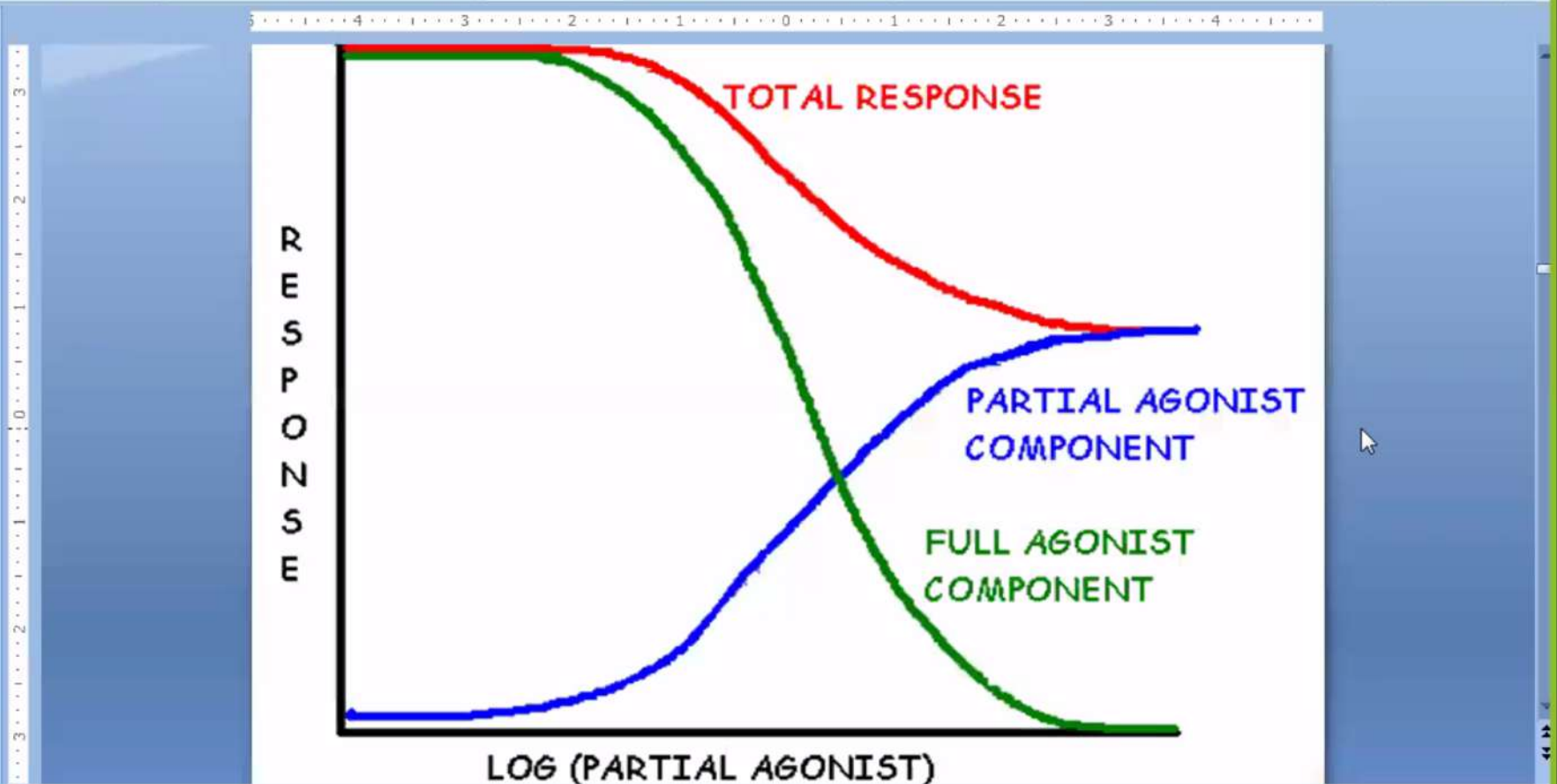
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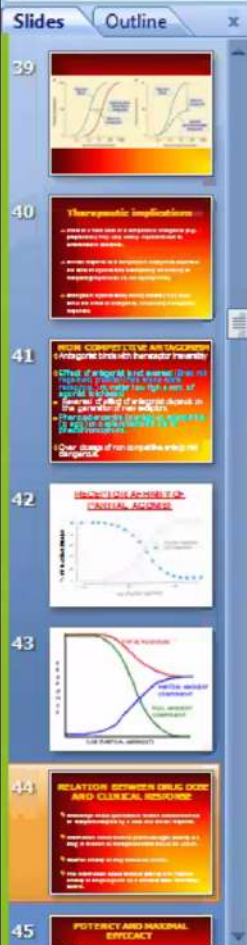
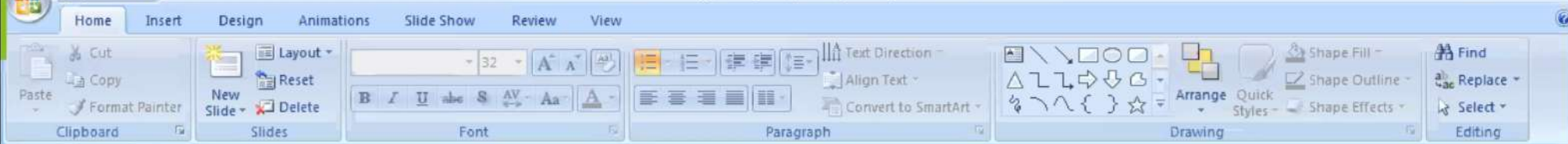
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- 39
- 40 Therapeutic Implications
- 41
- 42
- 43
- 44 RELATION BETWEEN DRUG DOSE AND CLINICAL RESPONSE
- 45 POTENCY AND MAXIMAL EFFICACY



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RELATION BETWEEN DRUG DOSE AND CLINICAL RESPONSE

- Knowledge about quantitative relation between number of receptors occupied by a dose and clinical response.
- Information about relative pharmacological potency of a drug in relation to therapeutic effect should be known.
- Maximal efficacy of drug should be known.
- The information about relative potency and maximal efficacy of drugs is given by a **GRADED DOSE RESPONSE CURVE**

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