Lecture 42

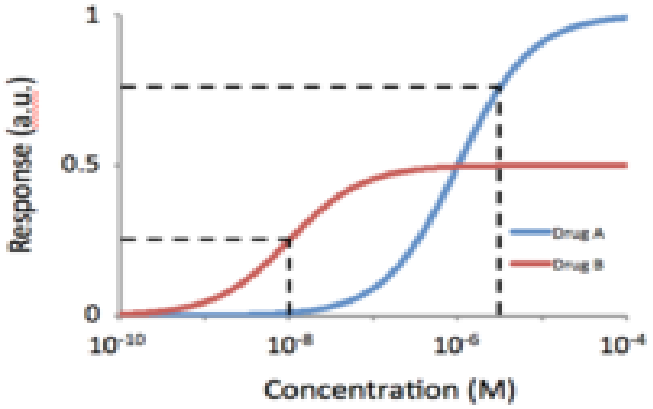
Properties of Drugs

Potency

Potency is a measure of drug activity expressed in terms of the amount required to produce an effect of given intensity. A highly potent drug (e.g., fentanyl, alprazolam, risperidone) evokes a given response at low concentrations, while a drug of lower potency (codeine, diazepam, ziprasidone) evokes the same response only at higher concentrations. The potency depends on both the affinity and efficacy.

Affinity is the ability of the drug to bind to a receptor. Efficacy is the relationship between receptor occupancy and the ability to initiate a response at the molecular, cellular, tissue or system level. The response is equal to the effect, or (E), and depends on both the drug binding and the drug-bound receptor then producing a response; thus, potency depends on both affinity and efficacy.

The E_{max} is the maximum possible effect for the agonist. The concentration of A at which E is 50% of E_{max} is termed the half maximal effective concentration and is abbreviated $[A]_{50}$, or more commonly EC_{50}. The term "potency" refers to the $[A]_{50}$ value. The lower the $[A]_{50}$, the less the concentration of a drug is required to produce 50% of maximum effect and the higher the potency.

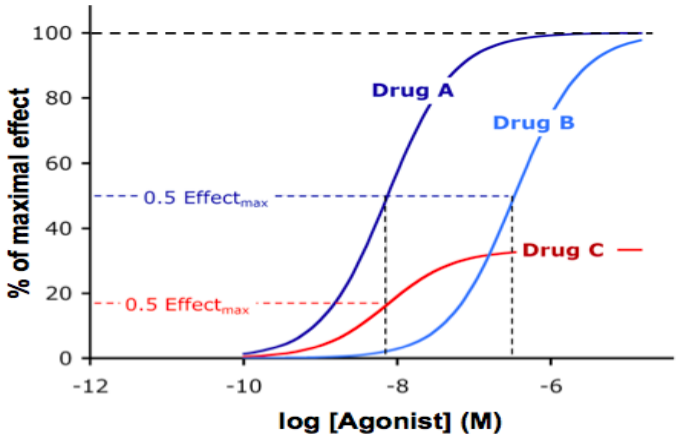


Efficacy

Efficacy (E_{max}) is the maximum response achievable from an applied or dosed agent, for instance, a small molecule drug. Intrinsic activity is a relative term that describes a drug's efficacy relative to a drug with the highest observed efficacy. It is a purely descriptive term that has little or no mechanistic interpretation.

In order for a drug to have an effect, it needs to bind to its target, and then to affect the function of this target. The target of a drug is commonly referred to as a receptor, but can in general be any chemically sensitive site on any molecule found in the body. The nature of such binding can be quantified by characterizing how tightly these molecules, the drug and its receptor, interact:

this is known as the affinity. Efficacy, on the other hand, is a measure of the action of a drug once binding has occurred. The maximum response, E_{max}, will be reduced if efficacy is sufficiently low, but any efficacy greater than 20 or so gives essentially the same maximum response.

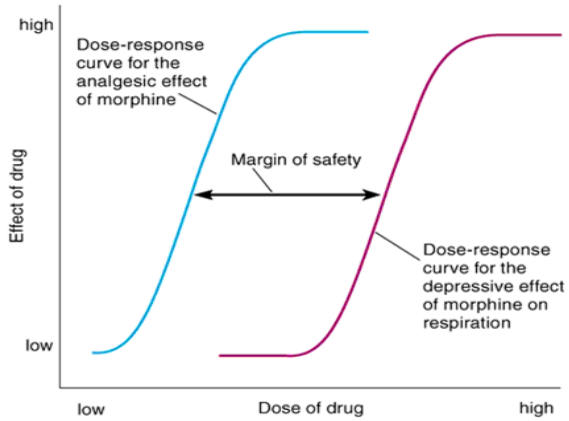


Tolerance

Tolerance describing subjects' reduced reaction to a drug following its repeated use. Increasing its dosage may re-amplify the drug's effects; however this may accelerate tolerance, further reducing the drug's effects. Drug tolerance is a contributing factor of drug addiction.

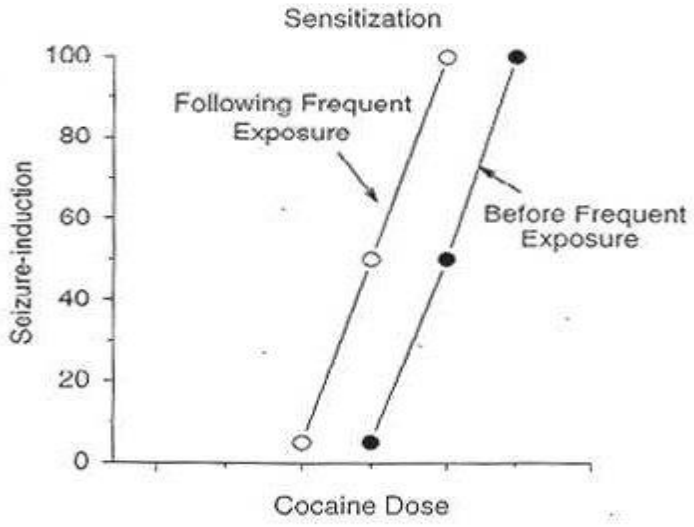
When drugs such as morphine are used repeatedly over time, tolerance may develop. Tolerance occurs when the person no longer responds to the drug in the way that person initially responded. Stated another way, it takes a higher dose of the drug to achieve the same level of response achieved initially. For example, in the case of morphine, tolerance develops rapidly to the analgesic effects of the drug.

► **Dose-Response Curves for the Analgesic and Depressant Effects of Morphine**



Sensitization

Sensitization is increased in a drug effect upon successive exposures to a drug or hypersensitivity to a drug in animals that were exposed to the drug in the past. For example, one unconditional effect of drugs such as amphetamine or cocaine is to produce psychomotor activation, often measured as an increase in forward locomotion. Under some circumstances repeated administration pshycostimulant drugs result in progressive increase in this drug effect whereby successive injections of the same dose produce greater and greater psychomotor activation. It is possible to develop tolerance to some side effects AND sensitization to other side effects of the same drug. Furthermore exposure to one drug eg amphetamine can also render animals hypersensitive to the locomotor activating effects of the other drugs eg cocaine or morphine.



Drug-drug Interactions

Drug-drug interactions occur when a drug interacts, or interferes, with another drug. This can alter the way one or both of the drugs act in the body, or cause unexpected side effects. The drugs involved can be prescription medications, over-the-counter medicines and even vitamins and herbal products.

In terms of efficacy, there can be several types of interactions between medications: cumulative, additive, synergistic, and antagonistic.

1. Pharmacodynamic interactions

The change in an organism's response on administration of a drug is an important factor in pharmacodynamic interactions. These changes are extraordinarily difficult to classify given the wide variety of modes of action that exist and the fact that many drugs can cause their effect through a number of different mechanism

2. Pharmacokinetic interactions

Modifications in the effect of a drug are caused by differences in the absorption, transport, distribution, metabolization or excretion of one or both of the drugs compared with the expected behaviour of each drug when taken individually.

Cumulative Effects

The condition in which repeated administration of a drug may produce effects that are more pronounced than those produced by the first dose. This is of frequent occurrence and is sometimes accidental, but is often caused deliberately by pushing a drug to its full physiologic effect. In cases in which this action occurs unexpectedly and is undesired, the drug should be immediately stopped, and not again given in doses that could cause such an effect.

Additive Effects

The effect of two chemicals is equal to the sum of the effect of the two chemicals taken separately, eg. aspirin and motrin.

Synergistic Effects

The effect of two chemicals taken together is greater than the sum of their separate effect at the same doses. E.g., alcohol and other drugs.

Antagonistic Effects

The effect of two chemicals taken together is less than the sum of their separate effect at the same doses.

Pharmacodynamics

Pharmacodynamics defined as the biochemical and physiological study of drug effects. These effects can include those manifested within mammals (including humans), microorganisms, or combinations of organisms (e.g. malaria infection). Pharmacodynamics places particular emphasis on dose-response relationships i.e. the relationship between drug concentration and effect. One dominant example is drug-receptor interactions as modeled by

$$L+R=L.R$$

where L, R, and LR represent ligand (drug), receptor, and ligand-receptor complex concentrations, respectively.

Agonism and Antagonism

Physiological agonism describes the action of a substance which ultimately produces the same effects in the body as another substance as if they were both agonists at the same receptor without actually binding to the same receptor. Physiological antagonism describes the behavior of a substance that produces effects counteracting those of another substance (a result similar to that produced by an antagonist blocking the action of an agonist at the same receptor) using a mechanism that does not involve binding to the same receptor.

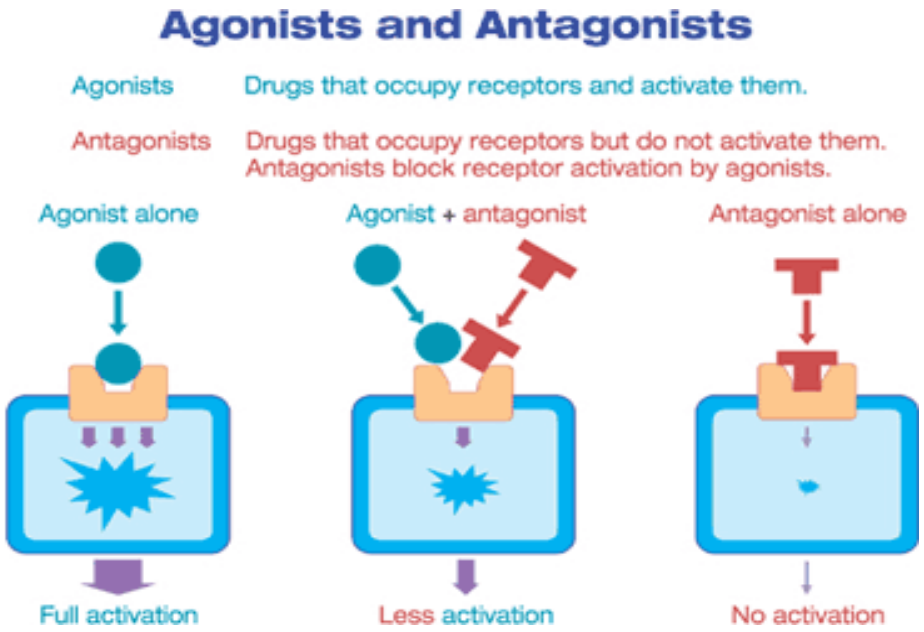
Modes of Action

1. Agonism

A compound that does the job of a natural substance. Does not affect the rate of an enzyme catalyzed reaction.

2. Antagonism

A compound inhibits an enzyme from doing its job. Slows down an enzymatically catalyzed reaction.



Law of Mass Action

A model to explain ligand-receptor binding. When a drug combines with a receptor, it does so at a rate which is dependent on the concentration of the drug and of the receptor. This model assumes that binding is reversible.

$$\text{Receptor} + \text{Ligand} \underset{K_{off}}{\overset{K_{on}}{\rightleftharpoons}} \text{Receptor} \bullet \text{Ligand}$$

Binding occurs when ligand and receptor collide due to diffusion, and when the collision has the correct orientation and enough energy. The rate of association is:

Number of binding events per unit of time =[Ligand]·[Receptor]·kon.

Equilibrium is reached when the rate at which new ligand×receptor complexes are formed equals the rate at which the ligand×receptor complexes dissociate. At equilibrium:

$$[\text{Ligand}] \cdot [\text{Receptor}] \cdot k_{on} = [\text{Ligand} \cdot \text{Receptor}] \cdot k_{off}$$

Meaning of Kd

Rearrange that equation to define the equilibrium dissociation constant Kd.

$$\frac{[Ligand]\cdot[Receptor]}{[Ligand\cdot Receptor]} = \frac{k_{off}}{k_{on}} = K_d$$

The Kd has a meaning that is easy to understand. Set [Ligand] equal to Kd in the equation above. The Kd terms cancel out, and you will see that [Receptor]/ [Ligand×Receptor]=1, so [Receptor] equals [Ligand×Receptor]. Since all the receptors are either free or bound to ligand, this means that half the receptors are free and half are bound to ligand. In other words, when the concentration of ligand equals the Kd, half the receptors will be occupied at equilibrium. If the receptors have a high affinity for the ligand, the Kd will be low, as it will take a low concentration of ligand to bind half the receptors

Applications of Drug Receptor Interaction

1. Drugs can potentially alter rate of any bodily/brain function.
2. Drugs cannot impart entirely new functions to cells.
3. Drugs do not create effects, only modify ongoing ones.
4. Drugs can allow for effects outside of normal physiological range.

References

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