Lecture 7

Pharmacodynamics

DOSE–RESPONSE RELATIONSHIPS

Agonist drugs mimic the action of the original endogenous ligand for the receptor (for example, isoproterenol mimics norepinephrine on β1 receptors of the heart). The magnitude of the drug effect depends on the drug concentration at the receptor site, which, in turn, is determined by both the dose of drug administered and by the drug’s pharmacokinetic profile, such as rate of absorption, distribution, metabolism, and elimination.

Graded dose–response relations

As the concentration of a drug increases, its pharmacologic effect also gradually increases until all the receptors are occupied (the maximum effect). Plotting the magnitude of response against increasing doses of a drug produces a graded dose–response curve that has the general shape. The curve can be described as a rectangular hyperbola, which is a familiar curve in biology because it can be applied to diverse biological events, such as enzymatic activity, and responses to pharmacologic agents. Two important properties of drugs, potency and efficacy, can be determined by graded dose–response curves.

Potency: Potency is a measure of the amount of drug necessary to produce an effect of a given magnitude. The concentration of drug producing 50% of the maximum effect (EC50) is usually used to determine potency. In Figure 2.7, the EC50 for Drugs A and B indicate that Drug A is more potent than Drug B, because a lesser amount of Drug A is needed when compared to Drug B to obtain 50-percent effect. Therapeutic preparations
of drugs reflect their potency. For example, candesartan and irbesartan are angiotensin receptor blockers that are used to treat hypertension. The therapeutic dose range for candesartan is 4 to 32 mg, as compared to 75 to 300 mg for irbesartan. Therefore, candesartan is more potent than is irbesartan.

The range of drug concentrations (from 1% to 99% of the maximal response) usually spans several orders of magnitude, semilogarithmic plots are used so that the complete range of doses can be graphed, the curves become sigmoidal in shape, which simplifies the interpretation of the dose–response curve.

**Efficacy:** Efficacy is the magnitude of response a drug causes when it interacts with a receptor. Efficacy is dependent on the number of drug–receptor complexes formed and the intrinsic activity of the drug (its ability to activate the receptor and cause a cellular response). Maximal efficacy of a drug (Emax) assumes that all receptors are occupied by the drug, and no increase in response is observed if a higher concentration of drug is obtained. Therefore, the maximal response differs between full and partial agonists, even when 100% of the receptors are occupied by the drug. Similarly, even though an antagonist occupies 100% of the receptor sites, no receptor activation results and Emax is zero. Efficacy is a more clinically useful characteristic than is drug potency, since a drug with greater efficacy is more therapeutically beneficial than is one that is more potent.

**Effect of drug concentration on receptor binding**

The quantitative relationship between drug concentration and receptor occupancy applies the law of mass action to the kinetics of the
binding of drug and receptor molecules:

\[
\text{Drug} + \text{Receptor} \rightarrow \text{Drug–receptor complex} \rightarrow \text{Biological effect}
\]

**Relationship of drug binding to pharmacologic effect**

The mathematical model that describes drug concentration and receptor binding can be applied to dose (drug concentration) and response (or effect), providing the following assumptions are met: 1) The magnitude of the response is proportional to the amount of receptors bound or occupied, 2) the E\text{max} occurs when all receptors are bound, and 3) binding of the drug to the receptor exhibits no cooperativity. In this case,

**INTRINSIC ACTIVITY**

- **Full agonists**
- **Partial agonists**
- **Inverse agonists**
- **Antagonists**

Antagonists bind to a receptor with high affinity but possess zero intrinsic activity. An antagonist has no effect in the absence of an agonist but can decrease the effect of an agonist when present. Antagonism may occur either by blocking the drug’s ability to bind to the receptor or by blocking its ability to activate the receptor

- **Competitive antagonists**
- **Irreversible antagonists**
- **Allosteric antagonists**
- **Functional antagonism**

**QUANTAL DOSE–RESPONSE RELATIONSHIPS**

Another important dose–response relationship is that between the dose of the drug and the proportion of a population that responds to it. These responses are known as quantal responses, because, for any individual,
the effect either occurs or it does not. Graded responses can be transformed to quantal responses by designating a predetermined level of the graded response as the point at which a response occurs or not. For example, a quantal dose–response relationship can be determined in a population for the antihypertensive drug atenolol. A positive response is defined as a fall of at least 5 mm Hg in diastolic blood pressure. Quantal dose–response curves are useful for determining doses to which most of the population responds. They have similar shapes as log dose–response curves, and the ED50 is the drug dose that causes a therapeutic response in half of the population.

**Therapeutic index**

The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity in half the population (TD50) to the dose that produces a clinically desired or effective response (ED50) in half the population:

\[
\text{TI} = \frac{\text{TD}50}{\text{ED}50}
\]

The TI is a measure of a drug’s safety, because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

**Clinical usefulness of the therapeutic index**

**Warfarin (example of a drug with a small therapeutic index):** As the dose of warfarin is increased, a greater fraction of the patients respond (for this drug, the desired response is a two- to threefold increase in the international normalized ratio [INR]) until, eventually, all patients respond. However, at higher doses of warfarin, anticoagulation resulting in hemorrhage occurs in a small percent of patients. Agents with a low TI (that is, drugs for which dose is critically important) are those drugs for which bioavailability...
critically alters the therapeutic effects

**Penicillin (example of a drug with a large therapeutic index):** For
drugs such as *penicillin*, it is safe and common to
give doses in excess of that which is minimally required to achieve
a desired response without the risk of adverse side effects. In
this case, bioavailability does not critically alter the therapeutic or
clinical effects