CHAPTER 2

Pharmacodynamics

CHAPTER OBJECTIVES

1. Define the term *pharmacodynamics.*
2. Identify what is represented by the frequency distribution curve.
3. Explain the dose–effect relationship.
4. Discuss how the therapeutic index of a drug is calculated.
5. Describe the affinity of a drug.
6. Identify various types of second-messenger events.
7. Briefly explain the four primary drug-receptor families.
8. Explain the equation used to calculate drug-receptor interactions.
9. Differentiate between agonists and antagonists.
10. Explain competitive and noncompetitive antagonists.

INSTRUCTIONAL GOAL: DEFINE THE TERM *PHARMACODYNAMICS.*

The text location of where the objective is met is on page 13.

Content Abstract

Pharmacodynamics is concerned with the pharmacologic actions of a drug, including both therapeutic effects and adverse effects. It describes how a medication causes changes in the body.

INSTRUCTIONAL GOAL: IDENTIFY WHAT IS REPRESENTED BY THE FREQUENCY DISTRIBUTION CURVE.

The text location of where the objective is met is on pages13 and 14.

Content Abstract

A frequency distribution curve represents the number of patients that respond to the actions of a drug at different doses. A few patients are shown to have responded to a medication at very low doses, whereas increasing numbers of patients responded as the dosage was increased. The median effective dose is shown at the top of the curve. It is important to understand that the frequency distribution curve does not indicate the magnitude of drug response, but does indicate if a measurable response occurred in the test group of patients.

INSTRUCTIONAL GOAL: EXPLAIN THE DOSE–EFFECT RELATIONSHIP.

The text location of where the objective is met is on page 13.

Content Abstract

The dose–effect (or dose–response) relationship is the relationship between the dose of a drug or other agent that produces therapeutic effects and the potency of these effects.

INSTRUCTIONAL GOAL: DISCUSS HOW THE THERAPEUTIC INDEX OF A DRUG IS CALCULATED.

The text location of where the objective is met is on pages14 and 15.

Content Abstract

The therapeutic index (TI) of a drug is used to predict whether a certain dosage is safe for a specific patient. It is calculated by dividing the median lethal dose (LD_{50}) by the median effective dose (ED_{50}).

INSTRUCTIONAL GOAL: DESCRIBE THE AFFINITY OF A DRUG.

The text location of where the objective is met is on page 15.

Content Abstract

A drug's affinity is its attractive force for a target receptor. The cell recipient is known as a receptor—usually a specific protein—situated either in cell membranes on cell surfaces or within the cellular cytoplasm. However, some drugs act on intracellular receptors; these include corticosteroids, which act on cytoplasmic steroid receptors.

INSTRUCTIONAL GOAL: IDENTIFY VARIOUS TYPES OF SECOND-MESSENGER EVENTS.

The text location of where the objective is met is on page 15.

Content Abstract

Once bound to a receptor, a drug may trigger second-messenger events inside cells. Examples include release of intracellular calcium, activation of enzymes and specific G proteins, and conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cyclic AMP).

INSTRUCTIONAL GOAL: BRIEFLY EXPLAIN THE FOUR PRIMARY DRUG-RECEPTOR FAMILIES.

The text location of where the objective is met is on pages 16 and 17.

Content Abstract

Enzymes are embedded in cell membranes. The ligand-binding domain is where drug and endogenous regulatory molecule binding occurs. It is on the cell surface, and catalytic sites of the enzymes are inside. Example: insulin.

Ligand-gated ion channels are receptors that span the cell membrane, regulating ions flowing in and out, with ion-specific channels. Channels open when an agonist drug or endogenous ligand binds the

receptor. Direction of flow is determined by the ion's concentration gradient. Examples: acetylcholine, GABA.

G protein-coupled receptor systems involve a receptor, a G protein, and an effector. Agonist drugs or endogenous ligands are bound. Examples: norepinephrine, histamine, serotonin, peptide hormones.

Transcription factors are located on DNA in the nucleus. They regulate protein synthesis with delayed responses. Activation requires highly lipid-soluble cell membrane ligands. Examples: thyroid hormone, all steroid hormones.

INSTRUCTIONAL GOAL: EXPLAIN THE EQUATION USED TO CALCULATE DRUG-RECEPTOR INTERACTIONS.

The text location of where the objective is met is on page 17.

Content Abstract

Drug-receptor interactions are calculated by the equation:

$$D + R \Leftrightarrow D\text{–}R \text{ Complex} \longrightarrow \text{Response}$$

INSTRUCTIONAL GOAL: DIFFERENTIATE BETWEEN AGONISTS AND ANTAGONISTS.

The text location of where the objective is met is on pages 17 and 18.

Content Abstract

An agonist is a drug that binds to a receptor and produces a stimulatory response that is similar to what an endogenous substance (such as a hormone) would have done if it were bound to the receptor. Agonist drugs have affinity, which allows them to bind to receptors, as well as high intrinsic activity, which allows them to activate the functions of receptors.

An antagonist is a drug or another agent that blocks or antagonizes the effects of another substance or function. Antagonists often compete with agonists for their receptor binding sites. Antagonists have almost no effects upon receptor function on their own.

INSTRUCTIONAL GOAL: EXPLAIN COMPETITIVE AND NONCOMPETITIVE ANTAGONISTS.

The text location of where the objective is met is on page 18.

Content Abstract

Most antagonists are classified as *competitive (surmountable) antagonists*. They bind reversibly to receptors, producing receptor blockade because they compete with agonists for receptor binding. The receptor will be occupied by which of the two agents is present in the highest concentration. The result can be "surmounted" (overcome) if the concentration gradient changes so that the opposite agent reaches a higher concentration.

There are also *noncompetitive (insurmountable) antagonists*. They bind irreversibly to receptors, effectively reducing the total amount of receptors that are available to be activated by an agonist. They reduce the *maximal response* that an agonist can trigger, and may completely block agonist effects if there is a high enough concentration of antagonist present. Noncompetitive antagonists cannot be overcome regardless of agonist concentrations, so they are rarely used therapeutically. Effects are not permanent, however, since receptors are replaced.

TEACHING STRATEGIES

1. Have students research articles about people who lost their jobs because of workplace drug testing.
2. Assign students different drugs and have them research therapeutic indexes.
3. Lecture on the actions of adenosine triphosphate and cyclic adenosine monophosphate.
4. Offer students a handout with a list of websites and printed resources that detail the release of new drugs into the marketplace. Source: www.centerwatch.com/drug-information/fda-approved-drugs.
5. Have each student research one example of an agonist, an antagonist, and an agonist-antagonist.

PRACTICAL ACTIVITIES

1. Give students the median lethal doses and median effective doses of 10 drugs, and have them determine each drug's therapeutic index.
2. Assign each student one popular drug and have them determine its frequency distribution curve.
3. Using diagrams, have students identify the locations of various cellular receptors.
4. Have students research the actions of insulin, and its use of enzymes embedded in cell membranes. Discuss.
5. Have students research the actions of histamine, and its use of G protein-coupled receptor systems. Discuss.
6. Ask students to research the most commonly used target molecules.

FACTOIDS

1. Drug-induced pharmacodynamic effects manifested in older adults include drug-induced renal toxicity, which can be a major factor when these adults are experiencing other kidney problems.
2. Lower drug doses for elderly patients should be used first, with titrations of the dose as tolerated to prevent unwanted drug-related pharmacodynamic effects.
3. There are major differences in the metabolism of morphine and the illegal drug heroin. Morphine mostly produces its CNS effects through m-receptors, and at k- and d-receptors. Heroin has a slight affinity for opiate receptors. Most of its actions are due to metabolism to active metabolites (6-acetylmorphine, morphine, and morphine-6-glucuronide).
4. Disorders that may affect pharmacodynamics include genetic mutations, malnutrition, thyrotoxicosis, myasthenia gravis, Parkinson's disease, and certain forms of insulin-resistant diabetes mellitus.

5. In women, pharmacodynamic differences include increased sensitivity to (and increased effectiveness of) beta-blockers, opioids, selective serotonin reuptake inhibitors, and typical antipsychotics.
6. Women are 50% to 75% more likely than men to experience an adverse drug reaction.