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In this textbook, reference to proprietary names of drugs is ordinarily made only in chapter sections dealing with preparations. Such names are given in SMALL-CAP TYPE, usually immediately following the official or nonproprietary titles. Proprietary names of drugs also appear in the Index.

...inetic ... York, 1984.
...er, D. *Pharmacokinetics*, 2nd ed. ... New York, 1982.
...R.; Hoyumpa, A.; Schenker, S.; and ... The effects of age and liver disease ...nd elimination of diazepam in adult ..., 1975, *55*, 347–359.
... G.; and Wilkinson, G. R. Altered ... and drug disposition. *Clin. Phar-* ... 135–155.
... Z.; and Graham, G. G. Clear- ...armacokinetics. *J. Pharmacokinet.* ... 123–136.
...armaceutics and Relevant Pharma- ...telligence, Hamilton, Ill., 1971.
...d Shand, D. G. A physiologic ap- ... drug clearance. *Clin. Pharmacol.* ...7–390.
...chke, T. F.; Meffin, P. J.; Melmon, ...d, M. Influence of acute viral hepa- ...and plasma binding of tolbutamide. ...ther., 1977, *21*, 301–309.

Pharmacodynamics may be defined as the study of the biochemical and physiological effects of drugs and their mechanisms of action. The latter aspect of the subject is perhaps the most fundamental challenge to the investigator in pharmacology, and information derived from such study is of basic utility to the clinician. The objectives of the analysis of drug action are identification of the primary action (as distinguished from description of resultant effects), delineation of the details of the chemical interaction between drug and cell, and characterization of the full sequence of actions and effects. Such a complete analysis provides a truly satisfactory basis for the rational therapeutic use of a drug on the one hand and for the design of new and superior chemical agents on the other.

MECHANISMS OF DRUG ACTION

While there are several types of exceptions, the effects of most drugs result from their interaction with functional macromolecular components of the organism. Such interaction alters the function of the pertinent cellular component and thereby initiates the series of biochemical and physiological changes that are characteristic of the response to the drug. This concept—now almost obvious—had its origins in the experimental work of Ehrlich and Langley during the late nineteenth and early twentieth centuries. Ehrlich was struck by the high degree of chemical specificity for the antiparasitic and toxic effects of a variety of synthetic organic agents. Langley noted the ability of the South American arrow poison, curare, to inhibit the contraction of skeletal muscles caused by nicotine; however, the tissue remained responsive to direct electrical stimulation. The terms *receptive substance* and, more simply, *receptor* were coined to denote the component of the organism with which the chemical agent was presumed to interact. There are fundamental corollaries to the statement that the receptor for a drug can be any functional macromolecular component of the organism. One is that a drug is potentially capable of altering the rate at which *any* bodily function proceeds; a second is that, by virtue of interactions with such receptors, drugs do not *create* effects but merely modulate ongoing function. A simple pharmacological dictum thus states that a drug cannot impart a new function to a cell. While modern technics of molecular genetics may challenge this principle, it remains valid for the immediate future (*see*, for example, Mishina *et al.*, 1985).

Whereas any functional macromolecular component of the organism may serve as a drug receptor, we will make special mention below of a group of cellular proteins that *normally* serve as receptors for endogenous regulatory ligands (*e.g.*, hormones, neurotransmitters). Many drugs mimic at least some of the effects of such endogenous compounds by interaction with the appropriate physiological receptor; such agents are termed *agonists*. In this context it is most important to note that other compounds may have no intrinsic regulatory activity at a given receptor but may still be able to bind to the macromolecule; a result of such binding may be interference with the effect of an agonist. Compounds that are themselves devoid of intrinsic pharmacological activity but cause effects by inhibition of the action of a specific agonist (*e.g.*, by competition for agonist binding sites) are designated as *antagonists*.

structural roles (*e.g.*, tubulin). Specific binding properties of other cellular constituents can also be exploited. Thus, nucleic acids are important drug receptors, particularly for chemotherapeutic approaches to the control of malignancy; plant lectins show remarkably specific recognition of carbohydrate moieties in glycoproteins (use of this property may be forthcoming in the synthesis of lectin-drug hybrids that are targeted to specific cells); drugs such as general anesthetics interact with and alter the structure and function of the lipids of cellular membranes.

The binding of drugs to receptors, in various cases, involves all known types of interactions—ionic, hydrogen, hydrophobic, van der Waals, and covalent. If binding is covalent, the duration of drug action is frequently, but not necessarily, prolonged. Noncovalent interactions of high affinity may also appear to be essentially irreversible. In most interactions between drugs and receptors it is likely that bonds of multiple types are important (*see* Goldstein *et al.*, 1974).

Structure-Activity Relationship. The affinity of a drug for a specific macromolecular component of the cell and its intrinsic activity are intimately related to its chemical structure. The relationship is frequently quite stringent, and relatively minor modifications in the drug molecule, particularly including such subtle changes as stereoisomerism, may result in major changes in pharmacological properties. Exploitation of structure-activity relationships has on many occasions led to the synthesis of valuable therapeutic agents. Since changes in molecular configuration need not alter all actions and effects of a drug equally, it is sometimes possible to develop a *congener* have profound effects on the pharmacokinetic properties of drugs.

Cellular Sites of Drug Action. The general and major determinants of the primary site of drug action must be the localization and functional capacity of the specific receptors with which the drug interacts and the concentration of drug to which the receptor is exposed. Localization of drug action is not necessarily dependent upon selective distribution of the drug. If a drug acts by interaction with a receptor that serves functions common to most cells, its effects will be widespread. If this is a vital function, the drug will be particularly dangerous to use. Nevertheless, such a drug may be clinically important. Digitalis glycosides, important in the treatment of heart failure, are potent inhibitors of an ion transport process that is vital to most cells. As such, they can cause widespread toxicity, and their margin of safety is dangerously low. Other examples could be cited, particularly in the area of cancer chemotherapy. Attempts have been made to restrict or direct the distribution of drugs by their attachment to soluble or insoluble carriers or by their encapsulation in liposomes. Another approach is the design of prodrugs that can be preferentially converted to the active species in only certain types of cells. These are areas of active investigation.

If a drug interacts with specialized receptors unique to specific types of differentiated cells, its effects are more specific. The hypothetical ideal drug would cause its therapeutic effect by virtue of such types of action. Side effects would be minimized, but toxicity might not be. If the differentiated function is a vital one, this type of drug could also be very dangerous. Some of the most lethal chemical agents known (*e.g.*,