Symposium on ocular pharmacology and therapeutics

TRANSACTIONS OF THE NEW ORLEANS ACADEMY OF OPHTHALMOLOGY

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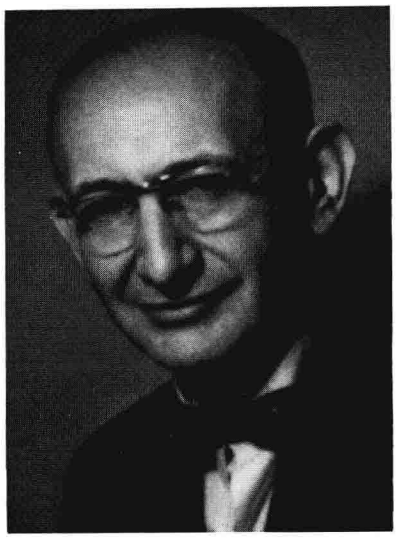

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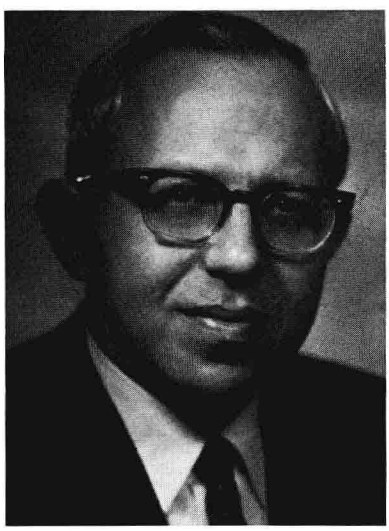

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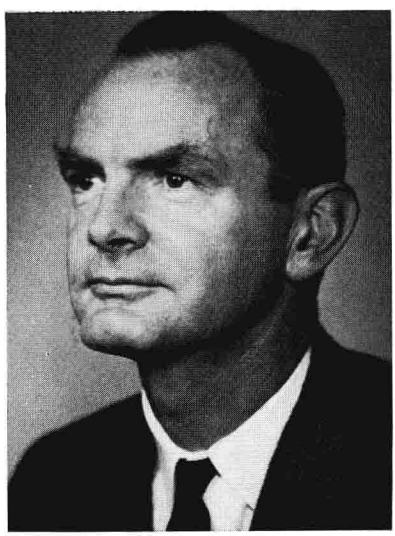

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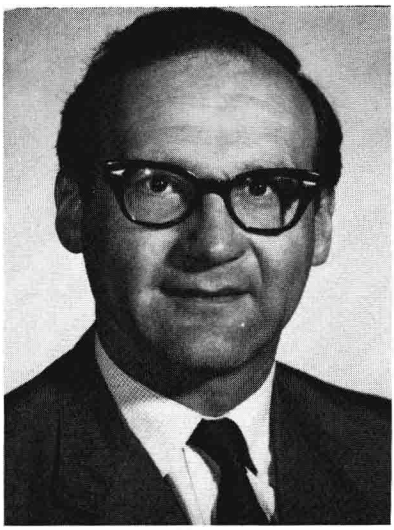

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Preface

Because of the great interest in drugs and their complications, the New Orleans Academy of Ophthalmology devoted its eighteenth annual session to the topic of ocular pharmacology and therapeutics.

The panelists of this Symposium are all ophthalmologists who have made outstanding contributions in this field of ophthalmology. The questions from the audience have been incorporated into the Round Table Discussions, which were very informative.

Symposium on ocular pharmacology and therapeutics

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*Ocular pharmacodynamics**

Kenneth T. Richardson

The study of the penetration, distribution, and response to pharmacologic agents is both fascinating and difficult. The ability of a drug to gain access to its site of action is determined in large part by its ability to be transferred across living membranes. The speed with which a molecule or ion is able to pass through a membrane relates to its lipid solubility, its electric charge, its molecular size and shape, and the presence or absence of a carrier substance within the cell membrane that effects its transfer. Once the drug has reached its site of action, its characteristic effect is commonly related to its chemical structure. The receptor theory of drug action implies that a high degree of molecular complementarity between the receptor site and the pharmacologic agent is required for the biologic specificity that most therapeutic agents exhibit. The action of pharmacologic agents is to increase or decrease the normal function of a cell, not to impart a new function to the cell. The sites of action of drugs may be directly on the effector cell or indirectly through a variety of mechanisms.

Drugs are distributed generally throughout the body, but they have relative differences in their concentrations in different body tissues or organs, depending upon their ability to penetrate living membranes and their specific affinities for certain tissues. Our knowledge of drug distribution and drug action has increased considerably in recent years, yet our ignorance in many of these areas continues to exceed our knowledge. With the logarithmic increase in the number of pharmacologic agents available, it is necessary for the physician to continuously review basic pharmacodynamics if he is to avoid therapeutic empiricism.

MEMBRANE TRANSFER

Our first insight regarding the character of living membranes was supplied by Overton in 1902. He suggested that the cell membrane was lipid in character since he was able to demonstrate that lipid-soluble substances penetrated the cell much more rapidly than did lipid-insoluble substances. Collander concluded that the lipoid

*Artwork by R. J. Avondo.

membrane, as suggested by Overton, did not completely explain membrane permeability since other workers had demonstrated that small lipid-insoluble molecules such as urea and water were able to pass through membranes. Collander suggested that the lipoid membrane contained multiple small water-filled pores, which he therefore described as a lipoid-sieve membrane. He concluded that lipid-soluble substances diffused through the lipoid portion of the membrane and that small water-soluble molecules and ions passed through the micropores of this lipoid-sieve membrane. Molecular size and shape of the lipid-soluble molecules are not important in determining their ability to transfer through a living membrane. However, those water-soluble molecules that are too large to pass through the membrane pores are either unable to transfer through the membrane or must be carried through the membrane by specific carriers located within the membrane itself. The process of lipid-soluble substances passing through a living membrane is termed *diffusion,* and the process of water-soluble substances passing through the pores of the membrane is termed *filtration.* Both diffusion and filtration are considered to be passive methods of membrane transfer; that is, they require no energy to effect the transfer. In contrast to this, the carrier system that transports primarily large lipid-insoluble molecules and certain ions such as sodium is considered to be an active transport system since it requires a definite expenditure of energy to effect the transport (Plate I).

Passive transfer

Diffusion (Plate I, *A*). Those lipid-soluble substances that penetrate the membrane as though it were a layer of lipoid material move across the membrane by a process known as *simple diffusion.* The rate of transfer is directly proportional to their concentration gradient across the membrane; and when such lipid-soluble substances attain a steady-state distribution across a living membrane, their concentration is the same on both sides of that membrane. Simple diffusion, therefore, depends entirely on lipid solubility and is unrelated to molecular size or shape. There are two basic categories of molecules that have a lipid solubility sufficient to allow them to penetrate living membranes in significant quantity: these are *nonpolar molecules,* such as steroids, and *undissociated weak organic acids* and *bases* (alkaloids), such as pilocarpine and atropine.

Certain molecules or portions of molecules are surrounded by rather strong forces of electric attraction. These forces are due to so-called *polar* groups, which make up part of the organic structure of the molecule. Polar groups are those such as —OH, —NH_2, —COOH, —SH, —NO_2, and others. They contain atoms with three pairs of electrons that contribute to the strong forces of attraction surrounding the portion of the molecule that contains the group. Hydrocarbon (—CH) radicals represent most of the nonpolar groups on organic molecules. The nonpolar groups, in contrast to the polar groups, have no forces of attraction surrounding them (Fig. 1-1). Lipids are primarily nonpolar, and lipid-soluble substances are correspondingly nonpolar. Those molecules with strong forces of attraction surrounding them (polar) are attracted to each other, and, similarly, those substances with no appreciable fields of force surrounding them (nonpolar) are readily miscible. In contrast, the strongly charged polar substances will not dissolve in, or pass through, a membrane consisting primarily of nonpolar uncharged molecules.

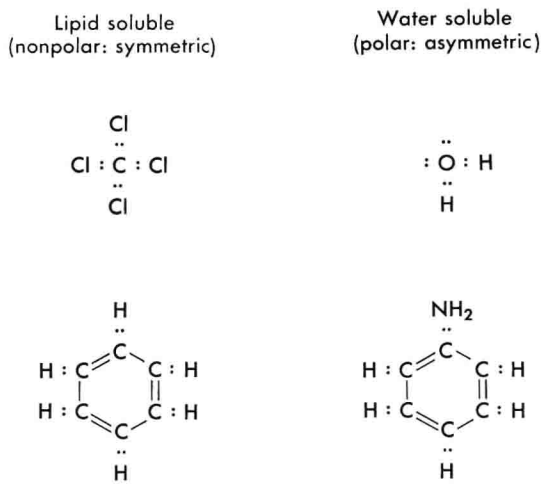

Fig. 1-1. Nonpolar substances are commonly symmetric and have no forces of attraction surrounding them. Hydrocarbon (—CH) radicals represent most of the nonpolar groups on organic molecules. Polar molecules are usually asymmetric, with strong forces of electric attraction. The radicals that represent most of the polar groups on organic molecules are —OH, —NH_2, —COOH, —SH, and —NO_2.

Nonpolar substances are commonly symmetric, such as benzene or carbon tetrachloride. If an —NH_2 group is substituted for a hydrogen atom on the benzene ring, the benzene ring will lose its symmetry, develop a force of attraction around the —NH_2 group, and become polarized. This will convert it from a nonpolar, lipid-soluble molecule to a polar, lipid-insoluble substance.

Water is a strongly polar molecule because of its —OH group; thus molecules that also contain strong polar groups are attracted to water and are termed *hydrophilic,* whereas those lipid-soluble substances containing nonpolar groups, primarily —CH, are *hydrophobic.*

Since living cellular membranes consist primarily of lipidlike (lipoid) molecules, they may be readily diffused by nonpolar pharmacologic agents such as steroids; but they will prohibit diffusion of polar, water-soluble pharmacologic agents such as penicillin and carbachol.

Certain weak organic bases (alkaloids) and acids are decidedly polar and water soluble when dissociated (ionized), but when undissociated (free base) behave as nonpolar molecules and thus are lipid soluble. This *biphasic solubility* is an important characteristic of a large group of ophthalmic therapeutic agents such as atropine, pilocarpine, and epinephrine (Plate I, *B*). The amount of a weak organic base that is dissociated depends on its dissociation constant (pK) and the pH of the surrounding medium. All acids owe their acid properties to the hydrogen ions present in their solutions, and the relative acidity of different acids is determined not by the concentration of the acid, but by the extent to which the acid molecules are ionized in solution and thus the amount of dissociated hydrogen ion available. In the case of weak or partially ionized acids, this comparison of acid strength can be quanti-

tatively expressed in the form of an ionization or dissociation constant. The same is true of weak bases. The amount of dissociation of any given weak acid or base depends on the pH of the medium in which the weak acid or weak base is located. Weak bases become progressively dissociated at a low pH and weak acids at a high pH. Considering that membrane permeability is limited to the weak organic bases in the undissociated state, the maximum penetration could be expected from those alkaloids (weak bases) whose dissociation is least at the physiologic pH. The pH at which physostigmine is 50% dissociated is 7.7, pilocarpine 7.1, and atropine 9.0. Therefore, approximately 50% of physostigmine and pilocarpine is available in the lipid-soluble, undissociated state at the physiologic pH. As illustrated, the dissociated and undissociated forms of these weak organic electrolytes exist in an equilibrium determined by their dissociation constant and the hydrogen ion concentration of the medium. As the undissociated lipid-soluble form penetrates the membrane and is effectively removed, the equilibrium continuously supplies undissociated lipid-soluble free base.

Some large organic molecules may have a portion that is hydrophilic, because of the presence of groups such as —OH or —NH_2, and another portion that is saturated with hydrocarbon radicals and consequently hydrophobic. Those molecules demonstrate considerable "surface activity" and arrange themselves so that the hydrophilic portion is oriented toward the water and the hydrophobic portion toward the lipid. Such surface-active molecules penetrate lipid membranes more effectively than do polar molecules that are not surface active. Pontocaine is a surface-active molecule that penetrates the corneal epithelium satisfactorily, whereas procaine has no surface activity and is unable to penetrate the corneal epithelium.

Filtration (Plate I, *A*). Water-soluble substances are unable to diffuse through the lipoid membranes and must be transferred through small water-filled pores and channels by a process known as *filtration*. In contrast to the process of diffusion, where molecular size is unimportant, both molecular structure and molecular size are of critical importance in the transfer of water-soluble substances through these small pores. In general, molecules with a molecular weight of less than 100 pass through the pores readily, those with molecular weights from 100 to 500 have an increasingly difficult time, and those greater than 500 are unable to pass through the water-filled channels. Thus, small molecules such as ethyl alcohol (mol. wt., 46) and urea (mol. wt., 60) pass with relative ease, whereas larger molecules such as glucose (mol. wt., 180), mannitol (mol. wt., 180), and penicillin (mol. wt., 256) are transferred very slowly. Small polar molecules penetrate the water-filled pores in part by random molecular motion and may also be swept through with a bulk flow of water. In addition to small molecules, many ions, particularly Cl^-, HCO_3^-, and H^+, are readily transferred passively through the water-filled membrane pores. Not all ions pass through these pores, however, in spite of their being water soluble and small; thus, sodium and potassium leak only very slowly through this membrane sieve.

The eventual distribution of the ions on either side of a semipermeable membrane will be determined by the Donnan equilibrium. Such an equilibrium exists when a membrane is permeable to ions but not to protein (that is, the protein carries a negative charge but is too large to pass through the micropores) and when protein, which acts as an anion, exists on only one side of the membrane. The potein molecule will act as a negative ion, and according to the Donnan theory of equilibrium:

(1) the product of the concentration of the sodium and chloride on one side of the membrane is equal to the concentration of these ions on the other side, and (2) the amount of sodium on either side equals the sum of the chloride and protein ions on the same side. Restated, the Donnan equilibrium determines the distribution of ions on either side of a semipermeable membrane that is permeable to some ions and impermeable to others. In biologic organisms the protein molecule is the most common anion to which the living membrane is impermeable.

The bulk flow of water through membrane pores occurs in response to the distribution of molecules and ions on either side of the membrane and the resulting osmotic forces. Water, itself, does not appear to be "pumped" through a membrane but passes readily through the membrane pores in response to an osmotic gradient.

It is possible to speed up the transfer of polar molecules and ions using electric current as an electromotive force. This technique is known as *iontophoresis* and has proved effective in aiding the transfer of penicillin and streptomycin through the intact cornea. It is also possible to increase the membrane penetration of highly polarized substances by applying surface tension–reducing molecules to the surface of the membrane. Benzalkonium applied to the corneal epithelium in sufficient concentration (0.03%) significantly increases the penetration of highly polarized surface-inactive agents such as carbachol.

Active transport (Plate I, C)

Certain ions and large water-soluble molecules are able to cross a living membrane against a concentration gradient and achieve a transfer speed that is inconsistent with their molecular size or known passive filtration rates. Such membrane transfer is achieved by a "carrier" located within the membrane itself and specifically involved with the active transport of a particular ion or water-soluble molecule across the membrane. Active transport is used to designate a process having the following characteristics: (1) the molecule or ion will move against a concentration gradient, (2) the transport mechanism has a definite limit as to the amount of solute that can be actively transported across the membrane and can become saturated if the concentration is raised sufficiently, and (3) the active transport mechanism requires energy to be expended and therefore can be inhibited by substances that interfere with cell metabolism. The solutes requiring active transport mechanisms are, in general, large polar molecules and certain ions.

Glucose is an important example of a large molecule that penetrates the cell primarily via an active transport (carrier) system. The intracellular glucose requirements are such that it would be impossible for a polar molecule as large as glucose to penetrate via the cellular pores in sufficient quantity to maintain cellular metabolism. Insulin appears to have an effect on this carrier system so that, in the absence of insulin, glucose is unable to enter the cell in adequate quantities. Both the sodium and the potassium ions are primarily transferred across the cellular membrane by an active carrier process whose energy is supplied by adenosine triphosphatase. Sodium leaking into the cell is continuously pumped out of the cell by this energy-requiring system; and, conversely, potassium leaking out of the cell is continuously pumped back into the cell. Thus, both potassium and sodium move against concentration gradients as they pass across cellular membranes; the metabolic pump maintains the high intracellular potassium and low intracellular sodium characteristic of

all cells. Considering the size of most organic pharmacologic agents, it is apparent that the rate of diffusion across biologic membranes can be correlated with the lipid solubility of the agent unless some active transport mechanism is involved. In the case of weak organic acids and bases, membrane permeability is limited to the nonionized (undissociated) form. The effective concentration available for diffusion of these weak organic acids or bases is therefore determined by the dissociation constant of the drug, the pH of the medium involved, and the lipid solubility of the undissociated molecule. In the evaluation of the pharmacologic activity of drugs, the routine determination of the relative water-lipid solubility and the ionization constant would be very helpful in predicting therapeutic pharmacodynamics.

CORNEAL PERMEABILITY

The corneal epithelium and endothelium both have the permeability characteristics of a typical cellular membrane; that is, they are penetrated readily by lipid-soluble substances and penetrated poorly by water-soluble substances unless these are small enough to pass through the cellular pores. The corneal stroma is readily penetrated by small polar water-soluble molecules and ions and, in addition, is reasonably well penetrated by nonpolar molecules. The solvent in which the drug is carried significantly affects the penetration of locally instilled ophthalmic medication. Nonpolar lipid-soluble drugs in an oil solution would enter the cornea slowly because of the affinity of the lipid-soluble substance to the oily solvent. Similarly, if a water-soluble drug is in aqueous solution, its penetration into the cornea is negligible. According to Swan, water-soluble polar compounds suspended in oil penetrated five to 13 times more readily than did aqueous solutions of equal concentration.

Steroids, chloramphenicol, and other lipid-soluble drugs penetrate the cornea readily, and significant aqueous concentration can be obtained by local instillation. Weak organic bases (alkaloids) such as atropine and pilocarpine are lipid soluble in their undissociated free-base form. At the physiologic pH of the corneal tear film, these alkaloids are 30% to 50% undissociated. Since the dissociated and undissociated forms exist in equilibrium as rapidly as undissociated molecules penetrate through the corneal epithelium, more are supplied from the dissociated ions as the equilibrium remains constant. Similarly, the undissociated molecule that has penetrated the epithelium and now lies in the stroma will dissociate in the stroma according to its dissociation constant at the pH of the stroma; the dissociated organic base will be transferred across the stroma to the corneal endothelium, where once again undissociated free base, which readily penetrates the endothelium into the aqueous, will be formed (Plate I, *B*).

With regard to the corneal penetration of a weak organic base, the pH of the ophthalmic solution is relatively unimportant since immediately upon local instillation the buffering capacity of the tears alters the pH of the ophthalmic solution to the normal physiologic pH. Therefore, the dissociation constant of the alkaloid is important only as it relates to the physiologic pH, not as it relates to the pH of the ophthalmic solution. A high proportion of commonly used drugs are capable of ionization somewhere within the physiologic pH range. Some of these, like sodium chloride, remain completely ionized within this range, but the great majority are similar to the alkaloids and ionize to different degrees as the pH is varied. This variable dissociation of drugs would not be a matter of great importance if both the ion and its non-