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Review

On the Mechanism of Absorption of Drugs from the Gastrointestinal Tract

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The question of how drugs pass from the gastrointestinal tract into the bloodstream is of vital interest to the pharmacologist and the medicinal chemist, but until recently little progress has been made in unravelling this seemingly complex problem. The literature abounds with reports of the absorption of drugs, but the studies are usually concerned with an evaluation of the rapidity and extent of absorption of a particular compound rather than with general principles. A survey of these reports fails to reveal significant clues concerning the mechanism of drug absorption mainly because so many different experimental procedures have been used. Drugs have been introduced into the gastrointestinal tract as solids, suspensions, or solutions; they have been administered orally, intraduodenally, rectally, into the pyloric-ligated stomach, or into various types of intestinal loops. The extent of absorption has generally been appraised indirectly by the speed of onset or degree of pharmacological action, or by the rate of appearance of the drug in plasma or urine; these criteria of absorption are complicated by the variables of drug distribution, metabolism, and excretion. The diversity of experimental methods has resulted in the accumulation of a large amount of data lacking a common basis for comparison.

A rational approach to the problem of drug absorption would be to compare the rates of absorption of a wide variety of compounds by a method which measured directly the disappearance of the drug from the gastrointestinal tract.

Physical Nature of the Barrier Between Blood and the Gastrointestinal Tract

Two distinct boundaries separate the gastrointestinal tract from the bloodstream: (1) the epithelial lining of the gastrointestinal lumen; and (2) the blood capillary wall which is situated close to the base of the epithelial cell. The epithelial lining probably constitutes the main barrier to the passage of solutes, since the capillary wall is a highly porous structure that is readily penetrated by all crystalloids.[1] The problem of the mechanism of drug absorption might therefore be best approached by considering the ways in which drugs might penetrate the epithelial lining of the stomach and intestine.

The question of how organic compounds cross the boundaries of living cells has always fascinated the biological scientist and has stimulated a vast amount of research. Although the problem is far from being solved, several ideas, arising from work of the past 60 years, have been combined into a useful working hypothesis about the nature of the cell membrane. Over 50 years ago, Overton[2] demonstrated that a number of organic compounds penetrate cells at rates roughly related to their lipid/water partition coefficient, and he concluded that the cell membrane is lipoidal in nature. Later, when it became apparent that the concept of a lipoid membrane did not explain the penetration into cells of small, lipid-insoluble molecules, it was postulated that solutes diffuse through the pores of a sieve-like membrane. The lipoid and sieve-like aspects of the membrane were combined by Collander and Bärlund[3] who pictured the cell boundary as a mosaic of lipid interspersed with tiny holes or pores; non-polar substances would penetrate the membrane by dissolving in the fat-like phase, and polar molecules would penetrate only if they were small enough to diffuse through the pores.

It soon became evident that this concept was inadequate to explain the rapid cellular transfer of certain relatively large, lipid-insoluble molecules like glucose. Höber[4] noted that the sugars which readily enter cells despite their lipid-insolubility are all normal cell substrates, and he used the term *physiological permeability* to describe the peculiar permeability of cells to these natural substrates. Later, the terms *active transport* and *facilitated*

diffusion were adopted to denote two different forms of this type of membrane penetration.

One view of *active transport* is that the solute crosses the membrane complexed with some membrane component or 'carrier'; the complex is formed on one side of the membrane, and split apart on the other side; the 'carrier' then returns to the membrane surface to complex with another solute molecule. Although the reports dealing with active transport are voluminous, and a number of models of the mechanism have been proposed, our knowledge of the process is mainly limited to a description of the characteristics which distinguish it from simple diffusion. These include: transport of solute against a concentration gradient or, if the solute is an ion, against the electro-chemical potential gradient; saturation of the transport mechanism when the concentration of substrate is raised high enough; specificity of the process for a certain molecular structure; competition between two substrates for the same transfer mechanism; and inhibition of the transport process by substances which interfere with cell metabolism. The term *facilitated diffusion* is used to signify a transport mechanism which shows all of the above characteristics except that the solute is not transferred against a concentration gradient.

Until recently, studies of the mechanism of gastrointestinal absorption have been concerned mainly with the absorption of organic nutrients and inorganic ions. This work has shown that certain sugars, amino acids, inorganic ions, and fats are absorbed by active transport mechanisms. So much attention has been directed toward metabolically dependent transport mechanisms that many workers have failed to distinguish specialized transport from passive transfer. Medicinal chemists and pharmacologists have tended to relegate to the background the early concepts of Overton and of Collander and Bärlund, that the cell boundary is essentially a lipoid-sieve membrane through which substances may or may not diffuse depending on their lipid-solubility and molecular size.

Possible Influence of Molecular Size and Lipid-Solubility on the Absorption of Some Non-Electrolytes

One of the first important studies dealing with the intestinal absorption of foreign organic compounds was that of Höber and

Höber[5] in 1937. These investigators found that mannitol, erythritol and glycerol are absorbed from intestinal loops of the rat at rates roughly proportional to the size of the molecules. A similar relationship was shown for the three aliphatic acid amides, succinimide, lactamide and acetamide. However, they noted that in each of these classes of compounds the rates of absorption could just as well be related to the relative lipid/water partition coefficients as to molecular size. Although they did not prove which of the two properties governs the rate of absorption, they felt that molecular size was the more important characteristic since the lipid-solubilities were so small.

Lipid-solubility was definitely implicated in absorption when these investigators compared the intestinal absorption of several compounds having appreciable lipid-solubilities. Valeramide, with an oil/water partition ratio forty times that of lactamide, was absorbed more rapidly than the latter compound despite its larger molecular weight. Moreover, succinimide and malonamide, compounds of similar molecular size, were absorbed at widely different rates in accordance with their relative lipid-solubilities.

Evidence was presented that the polyhydric alcohols and aliphatic acid amides are absorbed from the intestine by a process of simple diffusion. For example, the absolute amount of substance absorbed was directly proportional to the concentration, the percentage absorption remaining constant over a wide range of concentration. The gastric absorption of ethanol has also been shown to be a process of passive diffusion.[6]

These results suggest that some foreign organic compounds pass across the intestinal epithelium by simple diffusion through a lipoid-sieve type of boundary.

Importance of Dissociation Constant and Lipid-Solubility in the Absorption of Weak Organic Electrolytes

In applying physico-chemical criteria to the gastrointestinal absorption of drugs, it is necessary to take into account that most drugs are weak organic electrolytes, which exist in solution as a mixture of the dissociated and undissociated forms. This complicates the problem of describing the passage of drugs across a membrane, since usually only the undissociated forms are lipid-

soluble. The proportion of drug in the undissociated form depends on the dissociation constant of the compound and on the pH of the medium; consequently, to apply the lipoid membrane hypothesis to the absorption of drugs, it is necessary to know the dissociation constant of the drug as well as the lipid/water partition ratio of the undissociated form.

Absorption from the Stomach

A report by Travell[7] in 1940 gave the first indication that the gastric epithelium is selectively permeable to the undissociated form of a drug. In studying the absorption of strychnine and

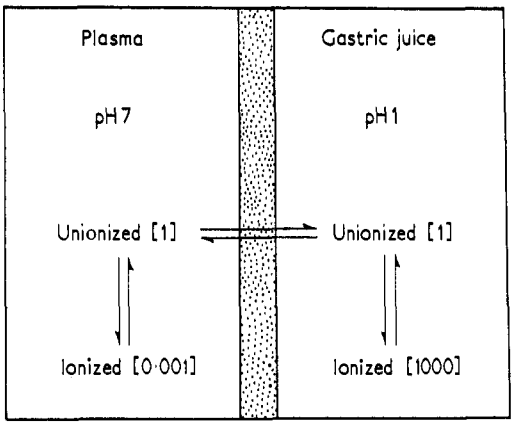

Fig. 1. Distribution of an organic base (pK_a 4) between plasma and gastric juice, assuming that the fluids are separated by a lipoid barrier

several other alkaloids from the pyloric-ligated stomach of the cat, Travell noted that large doses of the compounds in the stomach produced no toxic effects when the gastric contents were highly acidic. When the stomach contents were made alkaline, however, the drugs were readily absorbed and the animals killed. From a detailed study of strychnine absorption over a wide range of gastric pH values, it was concluded that the rate of absorption was dependent on the concentration of the undissociated drug molecule.

More definite evidence for the preferential permeability of the

gastric epithelium to uncharged drug molecules was supplied by the work of Shore *et al.*[8] These investigators administered drugs intravenously to dogs with Heidenhain gastric pouches, and determined the steady-state distribution of drug between gastric juice and plasma. A number of organic bases, partially to almost completely undissociated in plasma, entered the gastric lumen to yield gastric juice/plasma concentration ratios ranging from 1 to 40. In contrast acidic compounds, which were highly ionized in plasma, gave ratios of 0 to 0·6.

These results were shown to be consistent with a model system in which the gastric juice is separated from plasma by a barrier permeable only to the undissociated form of a weak electrolyte (Fig. 1). The steady-state distribution of a weak acid or base across such a barrier is given by the following equations:

$$\text{for an acid, } \frac{C_{GJ}}{C_{PL}} = \frac{1+10^{(pH_{GJ}-pK_a)}}{1+10^{(pH_{PL}-pK_a)}}$$

$$\text{and for a base, } \frac{C_{GJ}}{C_{PL}} = \frac{1+10^{(pK_a-pH_{GJ})}}{1+10^{(pK_a-pH_{PL})}}$$

where C_{GJ} is the concentration of drug in gastric juice, C_{PL} is that in plasma (corrected for protein binding), and pK_a is the negative logarithm of the acidic dissociation constant of the weak acid or base. From these equations, it can be readily calculated that a basic drug will be concentrated in gastric juice, but an acidic drug will be concentrated in plasma.

The concentration ratios observed in this study were generally in close agreement with the calculated ratios; however the maximum ratio of 40, observed for a number of basic compounds, was considerably less than the calculated value. This apparent inconsistency was resolved when it was shown that a gastric juice/plasma concentration ratio of 40 represented a limiting value imposed by the rate of gastric mucosal blood flow. In other words, the amount of drug transferred from plasma into gastric juice is limited by the rate at which drug is delivered to the gastric mucosa.

The observation that the gastric epithelium is permeable to uncharged drug molecules but relatively impermeable to ions led

Schanker and co-workers[9] to investigate the absorption of drugs from the stomach. A variety of compounds, dissolved in 0·1 N HCl solution, were introduced into the doubly-ligated rat stomach, and the degree of absorption was estimated from the amount of drug remaining in the stomach after one hour. Since weak acids are undissociated in the acidic gastric contents, and most weak bases are highly ionized, only the acidic compounds should be absorbed. In accord with this view, ready absorption was observed for all of the acidic drugs except the strong sulphonic

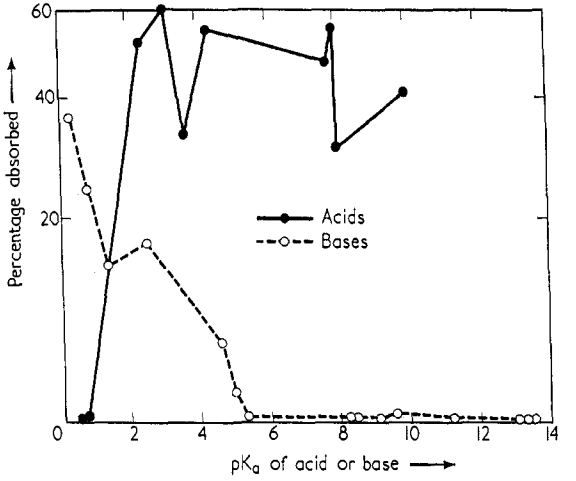

Fig. 2. Comparison between pK_a and gastric absorption of drugs in the rat

acids, which are ionized even in solutions of low pH (Fig. 2). Furthermore, none of the basic compounds were absorbed except those which are so weakly basic that they are partially undissociated in an acidic solution.

Further evidence that the gastric epithelium is selectively permeable to the un-ionized form of drugs was obtained by changing the proportion of drug in this form by raising the pH of the stomach contents with sodium bicarbonate. Basic compounds, which are more undissociated at higher pH values, were more readily absorbed from the alkaline gastric contents. In contrast, acidic compounds, which are more ionized at higher pH values, were less readily absorbed.

The importance of lipid-solubility in determining the rate of gastric absorption was shown in a study of three barbiturates of similar pK_a; these were absorbed at rates roughly proportional to the lipid/water partition coefficients of the undissociated drug molecules (Table I).

Table I. Comparison between gastric absorption of barbiturates in the rat and lipid/water partition coefficient (K) of the undissociated form of the barbiturate

Barbiturate	pK_a	% Absorbed	$K_{chloroform}$	$K_{heptane}$
Barbital	7·8	4	0·7	0·001
Secobarbital	7·9	30	23·3	0·10
Thiopental	7·6	46	>100·0	3·30

Hogben and co-workers[10] found that the pattern of absorption from the stomach of man was the same as that observed in the rat.[9] Acidic drugs, like salicylic acid, acetylsalicylic acid, thiopental, and secobarbital were readily absorbed. Basic compounds like quinine, ephedrine and aminopyrine were not absorbed. Of considerable interest was the observation that the salicylates and thiopental were absorbed more rapidly than ethyl alcohol; ethanol has often been cited as the unusual example of a drug that is absorbed from the stomach.

Absorption from the Small Intestine

Schanker and co-workers[11] demonstrated that the epithelium of the intestine is very much like that of the stomach in that it allows the ready penetration of undissociated drug molecules but is highly resistant to the passage of ionized moieties. In the experiments, the entire small intestine of the anaesthetized rat was perfused with drug solution, and the degree of absorption estimated by measuring the difference in the concentration entering and leaving the intestine.

A relation between the degree of ionization and the rate of absorption of drugs was revealed: the weaker acids and bases were readily absorbed; stronger, highly ionized organic electrolytes were slowly absorbed; and the completely ionized quaternary

ammonium compounds and sulphonic acids were hardly absorbed at all (Fig. 3).

The authors pointed out that the failure to observe any measurable absorption for some of the very highly ionized compounds was not inconsistent with the slow but definite absorption of these substances known to occur in therapeutics. In their experiments, the drug solution passed through the intestine in

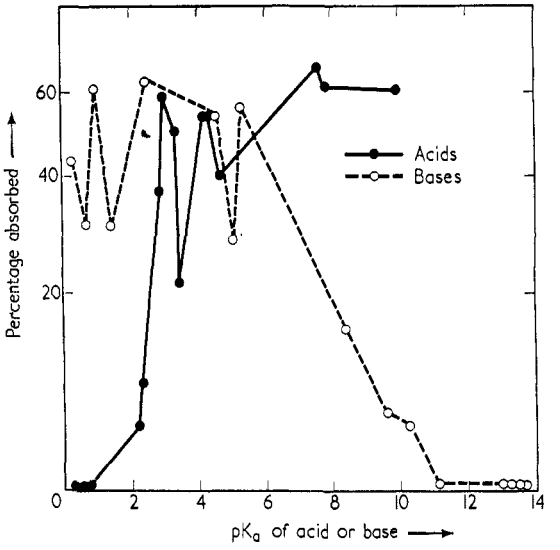

Fig. 3. Comparison between pK_a and intestinal absorption of drugs in the rat

only seven minutes, compared with the several hours that a drug remains in the intestine when used therapeutically.

The slow rates of absorption for many of the highly ionized compounds were magnified by continuously recirculating the drug solution through the intestine. Significant rates of absorption were thereby obtained for all of the drugs except the completely ionized quaternary ammonium compounds and sulphonic acids. These results suggest that a drug may be almost totally ionized, but can still be absorbed by passive diffusion because of the small concentration of lipid-soluble, undissociated molecules.

Since drugs like salicylic acid and aniline were absorbed at a

constant percentage over a wide range of concentrations, it may be presumed that these substances cross the intestinal epithelium by simple diffusion rather than by means of a saturable transport mechanism. Additional evidence of this is the failure of one drug to alter the rate of absorption of another. For example, when solutions containing various combinations of drugs were passed through the intestine, each compound was absorbed as though it were present alone.

Since the rates of absorption of drugs were related to the proportion of lipid-soluble, undissociated drug molecules and not to the molecular weight of the compounds, the main pathway of absorption appears to be through the lipoid areas of the intestinal boundary rather than through small pores. As evidence of this view, a number of lipid-soluble drugs of high molecular weight were absorbed more rapidly than small, lipid-insoluble molecules like D_2O and urea.

The pH of the intestinal contents determines the extent of ionization of a drug and should therefore be an important factor in dictating the rate of absorption. Hogben and co-workers[12] studied the effect of intestinal pH on the absorption of a number of weak organic acids and bases in the rat. In varying the pH of the drug solution from 4 to 8, the authors found that the rates of absorption varied directly with the proportion of drug present as the undissociated molecule. For example, raising the intestinal pH increased the absorption of bases and decreased the absorption of acids (Fig. 4). Furthermore, compounds which remained essentially undissociated at the various pH values showed no change in absorption.

For a more detailed study of the relationship between intestinal pH, the pK_a of a drug, and the rate of drug absorption, these investigators determined the steady-rate distribution of drugs between plasma and the intestinal lumen. In the experiments, the rat intestine was perfused with a solution of drug, and the animal also received the drug intravenously. At the steady state, when there was no net passage of drug from intestine to plasma or from plasma to intestine, samples of the intestinal solution and plasma were removed and analysed for the drug.

The observed gut/plasma concentration ratios agreed only roughly with the ratios calculated from the equations described

earlier. For example, when the measured pH values of the gut solution (6·6) and plasma (7·4) were substituted in the equations, the resulting ratios for acidic drugs were greater than the observed values, and those of basic compounds lower than the observed values.

These results suggested that the pH of the intestinal contents might not be the same as the effective pH at the site of absorption. From the observed concentration ratios, the authors calculated

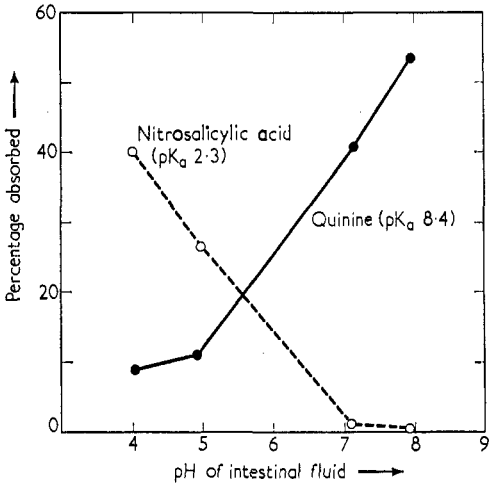

Fig. 4. Effect of intestinal pH on the absorption of an acidic and a basic drug

a hypothetical or 'virtual' intestinal pH; a value of 5·3 was obtained. An effective pH of 5·3, possibly located at the surface of the intestinal epithelial boundary, would explain an earlier observation[11] (see Fig. 3) that the lowest pK_a of an acidic drug consistent with very rapid absorption was about 3, while the corresponding highest pK_a for a basic drug was about 8. Assuming an effective pH of 5·3, the ratio of un-ionized to ionized drug necessary for very rapid absorption is 1:300 for both an acid of pK_a 2·8 and a base of pK_a 7·8. On the other hand, if the intestinal pH is accepted as 6·6, the necessary proportion of un-ionized to ionized drug is 1:6000 for acids and 1:16 for bases —an unlikely circumstance if the lipoid boundary concept is valid.

Evidence that lipid-solubility is the physical property that governs the passage of uncharged molecules across the intestine–blood boundary was provided by the observation that the rates of absorption of a large number of weak acids and bases were roughly parallel to the organic solvent/water partition ratios of the undissociated drug molecules (Table II).

Table II. Comparison between intestinal absorption of weak organic acids and bases in the rat and lipid/water partition coefficient (K) of the undissociated form of the compounds

Drug	% Absorbed	$K_{heptane}$	$K_{chloroform}$
Rapid rate of absorption			
Phenylbutazone	54	>100	>100
Thiopental	67	3·30	>100
p-Toluidine	56	3·26	97·5
Aniline	54	1·10	26·4
m-Nitroaniline	63	0·24	39·2
Benzoic acid	54	0·19	2·9
Phenol	60	0·15	2·3
p-Nitroaniline	61	0·13	19·8
p-Hydroxypropiophenone	61	0·12	5·1
Salicylic acid	60	0·12	2·9
m-Nitrobenzoic acid	50	0·06	2·6
Moderate rate of absorption			
Aminopyrine	27	0·21	>100
Acetylsalicylic acid	21	0·03	2·0
Acetanilide	43	0·02	7·6
Theophylline	30	0·02	0·3
Antipyrine	30	0·005	21·2
Barbital	25	<0·002	0·7
Theobromine	22	<0·002	0·4
Sulphanilamide	24	<0·002	0·03
p-Hydroxybenzoic acid	23	<0·002	0·01
Slow rate of absorption			
Barbituric acid	5	<0·002	0·008
Sulphaguanidine	<2	<0·002	<0·002
Mannitol	<2	<0·002	<0·002

Absorption from the Colon

Schanker[13] also studied the absorption of a number of drugs from the rat colon. The pattern of absorption observed in the colon was strikingly similar to that in the small intestine. Thus

weak acids and bases were in general readily absorbed; stronger acids and bases were more slowly absorbed; and quaternary ammonium ions and sulphonic acids were hardly absorbed at all. Moreover, the absorption of acidic drugs was increased, and that of basic drugs decreased, when the colonic contents were made acidic.

Lipid-solubility was again shown to be an important physical property in governing the rates of absorption of drugs. For example, nine barbiturates, having about the same pK_a values, were absorbed at rates roughly proportional to the chloroform/water partition ratios of the undissociated drugs (Table III).

Table III. Comparison between colonic absorption of barbiturates in the rat and lipid/water partition coefficient (K) of the undissociated form of the barbiturate

Barbiturate	% Absorbed	$K_{chloroform}$
Barbital	12	0·7
Aprobarbital	17	4·9
Phenobarbital	20	4·8
Allylbarbituric acid	23	10·5
Butethal	24	11·7
Cyclobarbital	24	13·9
Pentobarbital	30	28·0
Secobarbital	40	50·7
Hexethal	44	>100

Factors Involved in the Absorption of Organic Ions

Although the gastrointestinal absorption of weak organic electrolytes and non-electrolytes can be understood in terms of simple diffusion of uncharged drug molecules across a lipoid boundary, the question remains as to how organic ions are absorbed. The rates at which these anions and cations cross the gastrointestinal–blood barrier are certainly extremely slow compared with the rates of passage of uncharged molecules.[9, 11, 13]

Organic ions might penetrate the gastrointestinal–blood barrier in a number of ways: (1) by very slow diffusion through the lipoid areas of the barrier; (2) diffusion through a limited number

of large pores or through the spaces which might exist between the epithelial cells; (3) diffusion through the barrier in the form of a less polar complex formed with some material normally present in the lumen; (4) transfer across the barrier by a specialized transport process involving membrane 'carriers' or ion exchange mechanisms.

Levine and her co-workers[14,15] studied the absorption of a number of quaternary ammonium ions by measuring their rates of disappearance from loops of the rat small intestine. They observed that in general the rate of absorption declined markedly with time. For example, several quaternary ammonium compounds were absorbed to the extent of about 15 per cent in four hours, but most of the absorption took place during the first hour of the experiment. A possible exception is penthienate, which appeared to be continuously absorbed throughout five hours.[16] The authors suggested that the poor absorption of these drugs is due to the formation of non-absorbable complexes with mucin. This view was supported by the observation that adding mucin to the intestinal loop depressed the degree of absorption of benzomethamine.[14]

More recently Levine[17] reported that, although intestinal mucus may form non-absorbable complexes with quaternary ammonium compounds, removal of the mucus by washing the intestine results in a decrease rather than an increase in the absorption of these ions. It was suggested that the mucus might contain some component capable of forming an absorbable complex with these drugs. However, a variety of constituents of normal intestinal contents failed to augment the absorption of benzomethamine.[17] For example, adenylic acid, glucose-1-phosphate, chondroitin sulphate and hyaluronic acid were found to inhibit absorption; amino acids, saturated fatty acids, bile, bile salts, sorbitol, glucuronic acid, and mucic acid had no effect on the absorption of this drug.

The available information thus raises a number of questions about quaternary ammonium ion absorption. Does intestinal mucus promote as well as inhibit the absorption of quaternary ammonium compounds? If quaternary ammonium compounds are absorbed as complexes, what is the nature of the complex, and what happens to it on reaching the bloodstream? Do quater-

nary ammonium ions become involved in the ion transport processes responsible for the intestinal transfer of inorganic cations? And finally, how does the mechanism of absorption of these substances fit into the classical picture of membrane permeability? It is difficult to visualize mucus as responsible for the extremely slow passage of quaternary ammonium compounds across other living membranes such as the blood–cerebrospinal fluid barrier[18, 19] and the erythrocyte membrane.[18, 20]

Other Factors Affecting the Absorption of Drugs

Although this article concerns the mechanism by which drugs pass from the gastrointestinal lumen into the bloodstream, brief mention should be made of other factors which may modify absorption. For example, some drugs appear to be poorly absorbed, but actually are unstable in the gastrointestinal tract. Other compounds, especially acidic drugs, are absorbed slowly because they precipitate in the fluids of the stomach and intestine; their rate of solution now becomes the factor limiting the rate of absorption.

Numerous studies have shown that drugs are absorbed more slowly from suspensions or from solid dosage forms than from aqueous solutions. Advantage has been taken of this principle to prolong the pharmacological action of a drug. The so-called sustained-release pharmaceutical preparations have been reviewed recently.[21]

Physiological variables such as gastric emptying and the degree of intestinal motility can modify the rate of absorption of a drug. Foodstuffs within the stomach may interfere with absorption by adsorbing or binding a drug. The rate of gastrointestinal mucosal blood flow may possibly limit the rate of absorption in normal animals.

Conclusion

Studies in normal animals have contributed little to our understanding of the mechanism of drug absorption, mainly because of the inherent physiological variables and the difficulty in making quantitative estimates of the rate of absorption. Although the normal animal is extremely important in the final appraisal of the

absorption of a given compound, it is only when most of the physiological variables are eliminated and drugs are administered in true solution that the scientist clearly sees the two physical properties of drugs which are important in determining the rate of absorption: (1) the lipid/water partition ratio of the undissociated drug form; and (2) the dissociation constant, which determines the proportion of drug in this form. Thus weak organic acids and bases are readily absorbed when present as the lipid-soluble, uncharged molecule. Completely ionized drugs like the quaternary ammonium compounds and sulphonic acids are absorbed with great difficulty. Un-ionized substances with very low lipid-solubilities like sulphaguanidine are absorbed slowly. This may be explained on the assumption that the barrier between the gastrointestinal tract and the bloodstream behaves towards foreign compounds as a lipoid membrane.

With this information, the medicinal chemist is at last in a position to make predictions concerning the gastrointestinal absorption of drugs on the basis of known physico-chemical properties.

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