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Pharmacology of Intestinal Permeation II

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Preface

The intestine, particularly the small bowel, represents a large surface (in the adult human approximately 200 m^2) through which the body is exposed to its environment. A vigorous substrate exchange takes place across this large surface: nutrients and xenobiotics are absorbed from the lumen into the bloodstream or the lymph, and simultaneously, the same types of substrate pass back into the lumen. The luminal surface of the intestine is lined with a "leaky" epithelium, thus the passage of the substrates, in either direction, proceeds via both transcellular and intercellular routes. Simple and carrier-mediated diffusion, active transport, pinocytosis, phagocytosis and persorption are all involved in this passage across the intestinal wall.

The term "intestinal permeation" refers to the process of passage of various substances across the gut wall, either from the lumen into the blood or lymph, or in the opposite direction. "Permeability" is the condition of the gut which governs the rate of this complex two-way passage.

The pharmacologist's interest in the problem of intestinal permeation is twofold: on the one hand, this process determines the bioavailability of drugs and contributes significantly to the pharmacokinetics and toxicokinetics of xenobiotics; on the other hand, the pharmacodynamic effects of many drugs are manifested in a signigicant alteration of the physiological process of intestinal permeation.

The material in these volumes was collected in order to present some of the fundamental aspects of the permeability and the permeation of the intestine. An attempt has been made to include morphological, physicochemical, physiologic, biophysical, biochemical, pharmacologic and toxicologic aspects. Clearly, intestinal permeation cannot be properly studied from the perspective of one or a few disciplines; the subject cuts across a wide spectrum of disciplines. Consequently, it is hoped that the information provided in these volumes will be useful to scientists working in a variety of specialties.

I would like to express my thanks to those colleagues who accepted my invitation and contributed to this publication. It is somewhat unfortunate that the collection of the material required a considerable amount of time, but in a publication of this size, with a large number of contributors, some delay is inevitable. One prospective contributor was prevented from completing his task by a fatal heart attack, while others had to be excused because they failed to find enough time for the work. Fortunately, outstanding replacements were secured, but not without some holdup. Our knowledge of fundamental principles seldom changes in a revolutionary fashion, thus, despite the spread in time, it is hoped

that these volumes will provide the reader with the information necessary to form a correct contemporary image of the complex process of intestinal permeation and the conditions of permeability.

Finally, I would like to thank my wife for lending me a helping hand, admist her own professional duties, in various aspects of the editorial work.

T. Z. Csáky

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Intestinal Absorption of Xenobiotics

T. Z. CSÁKY

A. Introduction

A xenobiotic is a substance which is foreign to the living organism, but exposure to it affects the functions of the body. The effect can be therapeutically beneficial, i.e., pharmacologic, or harmful, i.e., toxic. The difference between pharmacologic and toxic action is more quantitative than qualitative. Essentially all therapeutically effective agents (drugs) can exert toxic effects in high enough doses. Consequently, in this chapter the expression "pharmacologic" will be used for basic properties of all xenobiotics, be they pharmacologic or toxic. Similarly, the expression "drug" will refer to xenobiotics in general. Several monographs have been published on the subject of drug absorption (BINNS 1964; HOUSTON and WOOD 1980; LEVINE 1971; PRESCOTT and NIMMO 1979).

B. Drug Absorption and Pharmacologic Response

According to modern pharmacologic concepts, the vast majority of drug actions are the consequence of an interaction between the drug and a specific bodily receptor. The microcosmos in the immediate vicinity of the receptor is called the biophase. Usually the quantitative action of given drug depends on its concentration in the biophase. This, in turn, is determined by pharmacokinetics, viz., the absorption, distribution, and elimination of the drug in the body. Thus, the absorption process ultimately influences markedly the quantitative action of all xenobiotics.

Most drugs act reversibly, i.e., at equilibrium the rates of formation and dissociation of the drug-receptor complex are equal. Moreover, these rates are so high that they parallel the changes of the concentration of the drug in the biophase and, in turn, in the tissue water. The latter is in rapid equilibrium with the concentration of the unbound drug in the plasma. Consequently, the quantitative action of many drugs is directly related to their concentration in the plasma (BRODIE and MITCHELL 1973).

In humans, the gastrointestinal absorption of a given drug or drug product is usually expressed by the term "bioavailability" which is a measure of the rate and extent to which a drug is transferred from the gastrointestinal tract to the systemic circulation. Bioavailability ist quantitated by the determination of the concentration of the drug in the blood plasma at given intervals following administration. Figure 1 indicates the information which can be obtained from the data. The following parameters are usually taken into consideration:

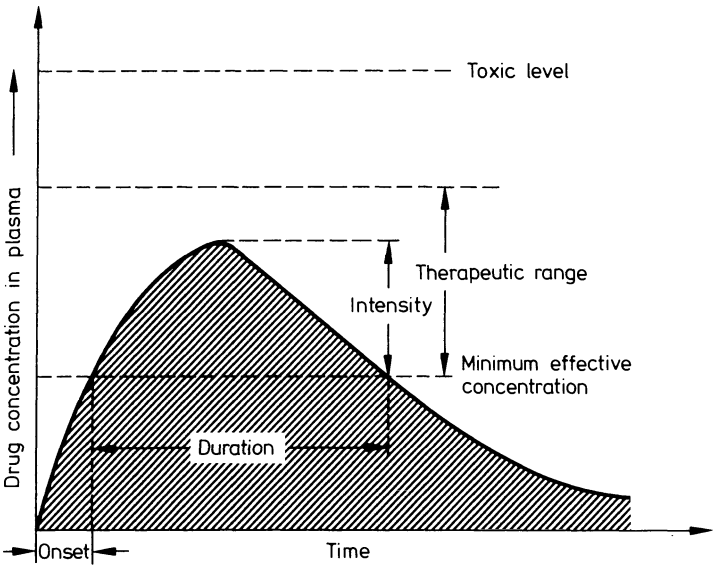

Fig. 1. Relationship between the effectiveness of the drug and its concentration in the blood plasma following oral administration. The AUC is shaded

1. The peak height to plasma or serum concentration.
2. The rate of absorption, i.e., the time between the administration and the achievement of the peak height concentration.
3. Total amount absorbed. This is measured from the area under the plasma or serum concentration–time curve and is expressed as AUC (area under curve).
4. Additional information can be obtained concerning the time needed for the onset, the duration, and the intensity of action.

Figure 2 illustrates how the variation of these parameters affects the quantitative action of the drug. Figure 2a depicts three hypothetical cases for the same drug in which the rate of absorption varied while the total amount absorbed (AUC) was unchanged. Figure 2b depicts three cases in which the rate was the same, but the fraction of the amount absorbed varied. Form the analysis of these cases it is clear that the drug absorption is of particular concern in cases of drugs, such as analgesics, spasmolytics, or antiasthmatics, which are administered in a single dose for the purpose of reaching rapidly a definite plasma concentration level. Within this category, particularly if the drug has a narrow margin of safety, monitoring the plasma level is advisable. On the other hand, in case of drugs which are given in multiple doses to achieve and maintain a relatively constant plasma level, the rate of absorption is less a determining factor, but the total amount absorbed (AUC) may be significant.

C. The Side of Drug Absorption

As will be seen, passive diffusion appears to be the most common process in the intestinal absorption of xenobiotics. In this process the rate is determined by the

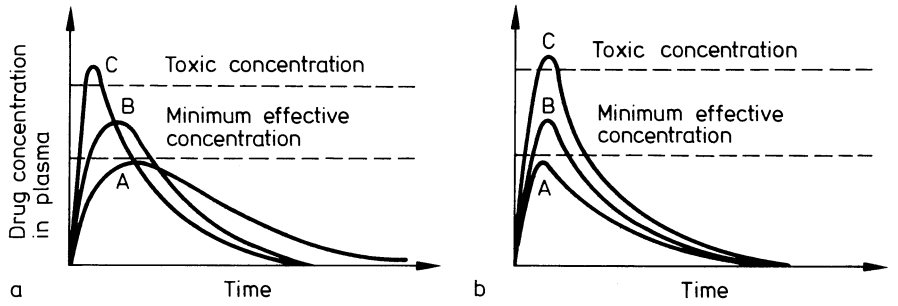

Fig. 2 a, b. Influence of the variation in the rate of absorption (**a**) and in the fraction of the amount absorbed (**b**) upon the pharmacologic effectiveness. **a** Three hypothetical cases for the same drug in which the rate of absorption varied while the total amount absorbed (AUC) was unchanged. *A*, Drug level did not reach therapeutic effectiveness; *B*, therapeutic level was achieved; *C*, toxic level was obtained. **b** Three cases in which the rate was the same, but the fraction of the amount absorbed varied. *A*, Therapeutic level not reached; *B*, therapeutic level reached; **C**, toxic level obtained. *Broken lines,* the minimum blood level at which therapeutic or toxic effects, respectively, are achieved

area of the absorptive surface and the concentration difference between the lumen and the bloodstream. In the gastrointestinal tract the small intestine represents the largest absorptive surface, about 200 m^2 in an adult human (WILSON 1962), and is endowed with an abundant blood supply. Because of its much larger surface and better blood supply, the small intestine plays a significantly greater role than the stomach in the absorption of xenobiotics. This is true even with drugs which are fat soluble,such as ethanol(MAGNUSSEN 1968), or with weak acids, e.g., aspirin (SIURULA et al. 1969), which in the acid stomach are nonionized, thus becoming lipid soluble. Drugs and other xenobiotics can be absorbed also from the large intestine which represents a smaller area with less abundant blood supply. In living subjects after oral administration the drug absorption from the small intestine is sufficiently vigorous so that little reaches the large intestine.

Lipid-soluble drugs are readily absorbed from the rectum. The principal difference between intestinal and rectal absorption is that the veins from the intestine empty into the portal circulation, while the blood from the rectum is carried to a large extent through the hemorrhoidal veins into the vena cava, thus bypassing the liver. However, in humans this is not so clear-cut: a venous plexus collects the blood from the mucosa of the rectum. From this the upper hemorrhoidal veins carry the blood into the portal system, while the lower hemorrhoidal veins empty it via the iliac veins into the vena cava. Thus, in humans part of the rectally absorbed drug may end up in the portal system and part will be transported directly into the inferior vena cava. The situation is further complicated by individual variations which render the prediction of the circulatory fate of the rectally administered drug rather uncertain (DE BOER and BREIMER 1979).

D. The Intestinal Barrier and its Permeability

One can consider the intestine as a complex biologic membrane: it is composed essentially of the mucosal epithelial cells, the tight junction and intercellular