# DRUG DESIGN

edited by E. J. Ariëns

Volume II


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# Chapter 1 Modulation of Pharmacokinetics by Molecular Manipulation

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## I. Introduction

Drug design, as a rule, starts with a known bioactive compound, the mother compound, as a lead.

The main objectives of molecular manipulation in drug design are:

1. Modulation of the action in the strict sense of the mother compound. This implies elimination of particular components from the spectrum of action, conversion to antagonistic compounds, and possibly increase in potency.

2. Modulation of the pattern of action by modulation of the pharmacokinetics. This may concern realization of a particular time–response relationship, selectivity in action and possibly increase in potency (*17*). Often the aim is the development of compounds adapted to the specific requirements for optimal dosage regimens for therapeutics, application regimens for pesticides, etc.

In this chapter the modulation of pharmacokinetics by molecular manipulation will be discussed. In contrast to pharmaceutical formulation, in which the composition of the mixture used as the application form is adapted, here the term chemical formulation may be used indicating that the bioactive compound itself is adapted chemically. The design of drug mixtures (*299*) is a field of action for pharmacologists and pharmacists, not for the medicinal chemists who perform molecular manipulation (*17*).

For biological activity two types of chemical requirements can be differentiated (*11, 12, 13*):

1. The requirements for biological activity in the strict sense. These are the chemical properties necessary for the induction of the effect on the level of the specific receptors or sites of action (*17*).

2. The requirements for pharmacokinetics of the bioactive compounds. These are the chemical properties necessary for the uptake, transport, chemical conversion, and elimination of the drug. In general, the properties of the drug which determine the distribution over the multicompartment systems involved in individual and environmental pharmacokinetics (*17*).

In the efforts to modulate pharmacokinetics including environmental pharmacokinetics (*17*) there are two main approaches:

1. Modification of the characteristics of the biological or environmental multicompartment system. This may happen by modification of the capacity of the compartments for the drug, its transport mechanisms governing the uptake in, the exchange between and the elimination from the various compartments, and by modification of the turnover capacity of the processes governing its biochemical transformation involved in bioinactivation or bioactivation. This approach will not be discussed here. The reader is referred to the literature (*7, 13, 21, 22, 55, 74, 78, 80, 92, 179, 291, 321, 341, 346*).

2. Modification of the properties of the bioactive agent by modifying its partition coefficients or its affinity constants with respect to the various compartments, of the properties determinant for transportation, thus modifying its uptake in, exchange between, and elimination from the various compartments, and of the properties determining its sensitivity to biochemical conversion, i.e., bioinactivation or bioactivation. This in fact implies a modulation of the biological or physiological availability of the bioactive compounds by molecular manipulation (*15*, *16*).

The design of new compounds with chemical properties adapted to particular requirements with regard to pharmacokinetics opens wide perspectives.

On certain part-processes involved in pharmacokinetics, such as protein binding and enzymic biodegradation, information can be obtained from *in vitro* studies. Species differences for biological activity including toxicity of pharmaca appear more often to be due to differences in the pharmacokinetics, especially differences in the biodegradation, than to differences in biological activity in the strict sense (*46*, *47*). The design of bioactive compounds for application as therapeutic, food additive, pesticide, or whatever, will usually imply a compromise. The chemical properties required in one respect may be incompatible with those required in other respects. In the compromise the desiderata for pharmacokinetics as well as for the action and activity in the strict sense may be involved. As a rule the degree of freedom in molecular manipulation will be largest for pharmacokinetics. The drug distribution is mainly dependent on overall properties of the compound, such as partition over lipid/water phases, polarity, etc. The induction of the response, the drug–receptor interaction, often requires particular sterical properties and a particular charge distribution in the bioactive compound (*10*).

## II. The Significance of the Chemical Structure of Bioactive Compounds with Regard to the Various Processes Involved in Pharmacokinetics

Efforts to modify the chemical structure of a bioactive compound in such a way that only or mainly its pharmacokinetics and not its pharmacological action in the strict sense are changed, imply a restriction of the chemical modification to particular groups or moieties of the molecule. The aim is modification of the chemical characteristics essential for one particular aspect of the biological action. This requires some insight into the relationship between structure and action, especially with regard to the various processes involved in pharmacokinetics (*13*, *17*, *343*).

With respect to the pharmacodynamic action of bioactive compounds rules for structure–action relationship are restricted to particular types of

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drugs. Chemical requirements can be formulated for the group of the cholinergic agents, histaminergic agents, indirectly acting anticoagulants, β-adrenergic agents, for the group of the tolbutamide-related oral antidiabetics, etc. The requirements are specific for each group or type of drugs and hold true only within that group.

The rules for the relationship between structure and pharmacokinetic properties may be expected to be characteristic for the particular steps or part-processes in pharmacokinetics and not necessarily dependent on the particular type of pharmacological action of the drug. For each of the part-processes, such as passive distribution, metabolic conversion, and active excretion, particular rules will hold true. For one compound different rules obtain, depending on the part-process concerned. These rules, however, have a more or less general character since they do not differ for the different types of drugs. Such rules are of special importance in efforts to modulate pharmacokinetics of bioactive compounds by molecular manipulation.

What can be said about the chemical structure of bioactive compounds in relation to the various part-processes in pharmacokinetics?

1. For the absorption in the biological object and the distribution over its various compartments if based on free diffusion of the drug molecules through hydrophilic and lipophilic media and through pores, the overall physicochemical character of the drug is determinant. This character is the resultant of such properties as hydrophility, lipophility, polarity, size and shape, degree of ionization, etc. These properties in turn are the resultant of the contributions by the various parts or groups in the drug molecule. The balance between hydrophility and lipophility strongly depends, for instance, on the character of the various groups in the drug molecule. Also the localization of the groups, as in the case of substituents in aromatic nuclei, is of influence. Particular groups or moieties, such as highly ionized groups may play a predominant role. Consequently, for absorption, distribution, and excretion, insofar as these are processes based on free diffusion, certain general rules will hold true independently of the specific type of action of the drug. Strong bases or strong acids which are ionized for 100% will not, or only with difficulty, pass the various lipid membranes. They will restrict themselves in their distribution mainly to the extracellular compartment and will not or hardly penetrate the blood–brain barrier. For weak bases and acids distribution will be dependent on the degree of dissociation and therefore on the pH (Fig. 1). Strongly lipophilic compounds will accumulate in tissues rich in lipids (*10, 35, 48, 49, 234, 236, 293, 306, 326*).

2. The binding of the drug to more or less indifferent sites of binding on plasma proteins, mucopolysaccharides, and other body constituents also plays a role in its distribution. Although this binding to sites of loss, also called silent receptors (*336*), is related to the chemical properties of the drug

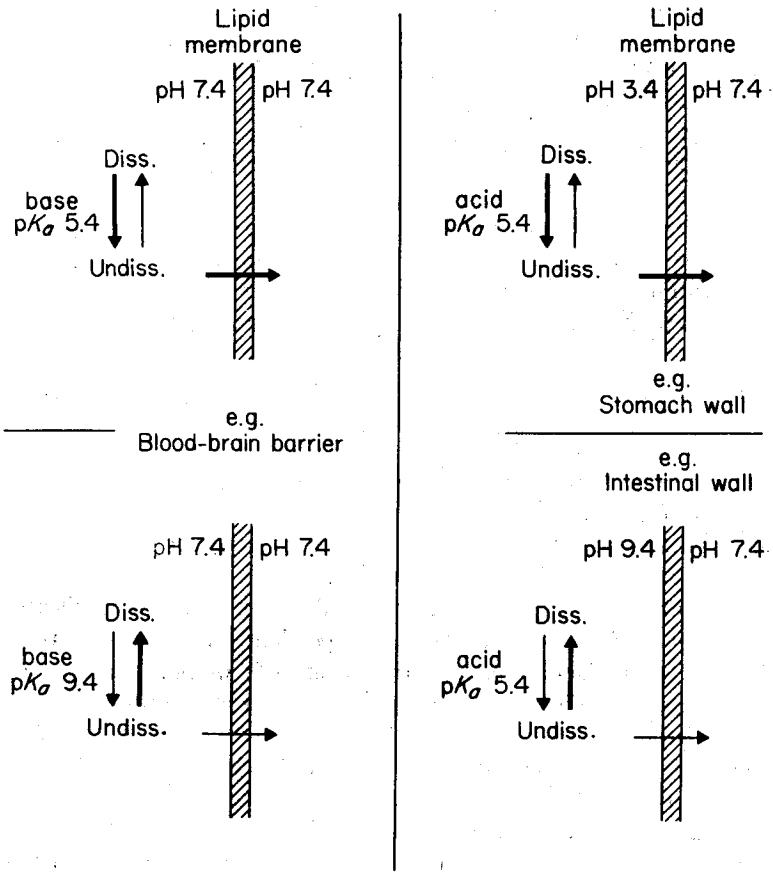


**Fig. 1.** Schematic representation of the influence of p$K_a$ differences (left) and pH differences (right) on the penetration of lipid membranes by weak bases and acids.

molecule, as a rule the structural requirements for this type of binding are not very high (*201, 202, 252, 292*). This means that a great variety of compounds, as long as they have certain trivial chemical features such as, for instance, an anionic or a cationic group, and a hydrocarbon body, will be bound to, and possibly will compete for, common sites of binding, on, e.g., plasma proteins, irrespective of their specific pharmacological action (*17, 24a, 63, 127, 135, 157, 188, 223, 247, 252, 318*). Consequently also in this case certain general rules can be expected. Examples are the binding of drugs to plasma proteins which results in a mutual interference of drugs by displacement from common binding sites (*15–17*) and the binding of onium compounds

such as curare to the acidic mucopolysaccharides. The consequence is that, for instance, curariform drugs may be potentiated by noncurariform bases as a result of the displacement of the curariform drug by these bases from such nonspecific binding sites (*63*).

3. If specific transport processes are involved which require binding of the drug to specific sites, for instance, on carrier molecules, the structure of the drug or the presence of particular groups in the drug molecule are important. Each specific transport system will have its own specific requirements with respect to the structure of the drug molecules transported. This implies a restriction in the applicability of the rules for structure and action that can be derived in this respect. In some cases the transport mechanisms are not highly selective, as, for instance, the system taking care of active excretion of a variety of organic acids and the system taking care of the active excretion of a variety of organic bases in the urine by the kidney and in the bile by the liver. Here certain general relations hold true, irrespective of the pharmacological character of the compounds involved. The acid-excreting system of the kidney, for instance, acts on certain types of organic acids such as antibiotic penicillin, radiopaque iodopyracet, diagnostic phenol red, and uricosuric probenecid (*33*, *34*, *35*, *112*, *165*, *258*, *267*, *292*).

4. For metabolic changes in drugs, too, rules with a general applicability hold true. This means that they are not dependent on the specific type of action of the drug. Determinant is the occurrence of particular chemical groups in the drug molecule. If a drug contains an ester group, it may be hydrolyzed by plasma esterases or other esterases in the body independent of the pharmacological group to which the compound belongs. Local anesthetics, parasympatholytics, curariform drugs, and general anesthetics may, if containing a suitable ester group, be hydrolyzed by these esterases (*10*). Whether hydrolysis takes place is dependent on the characteristics of the ester moiety and not on the type of action of the drug (*10*, *53*, *152*, *192*, *218*, *224*, *304*, *322*). The same holds for a number of other metabolic conversions such as oxidation of amines (*298*), reduction of azo compounds, and conjugation reactions (*10*, *132*). The consequence is that also here general rules may be derived.

It can be concluded that for a number of fundamental steps in pharmacokinetics such as distribution and metabolic changes, rules may be derived for structure–action relationships applicable to drugs in general, irrespective of the specific type of effect induced by these drugs. For the final step, the induction of the specific effect, the rules for structure–action relationship will be restricted in their applicability to drugs with a particular type of action. Further elucidation and analysis of the more general rules mentioned will be fruitful for drug design, especially with regard to the efforts to modulate pharmacokinetics by molecular manipulation.

In this respect the analysis of the relationship between biological properties of drugs and their physicochemical properties on the basis of substituent constants as worked out in much detail by Hansch may be rewarding (*17, 145–148*). A regression analysis with respect to the various aspects of bioactivity, such as the activity in the strict sense to be tested on simple isolated test systems, the capacity to penetrate tissues, measured, e.g., by absorption experiments, the metabolic conversion tested in *in vitro* studies, etc., might indicate which type of molecular manipulation (substituents) may be expected to be most promising. The aim is the synthesis of new compounds with pharmacokinetics modulated as required but under maintenance of the pharmacological action.

## III. Dissection of the Drug Molecule in Biofunctional Moieties

In the dissection of drug molecules into chemical groups or moieties, two approaches are possible. One can dissect the drug molecule into chemical groups on the basis of their contribution to the forces at action between drug and environment and more particularly between drug and receptor, such as the ionic groups, dipoles, inducible dipoles, groups able to contribute to hydrogen bonds, groups which contribute through van der Waals forces, and groups that contribute by means of hydrophobic aggregation forces (*131, 163, 270*). These may be called *chemofunctional moieties*. On the other hand, one can dissect the drug molecule on a more biological basis, namely by the distinction between various moieties on the basis of their significance for or predominance in particular aspects of the biological activity. These may be called *biofunctional moieties* (*11, 13, 14, 17, 122, 231*) (Table I).

The differentiation of the various biofunctional moieties has as a background the aim to modify certain biological properties or certain steps in the action

TABLE I
BIOFUNCTIONAL MOIETIES

| | |
|---|---|
| *Conducting moieties*<br>Moieties influencing the distribution of the drug in its active form over the various compartments | *Temporizing moieties*<br>Moieties influencing the time–concentration relationship of the drug in its active form |
| *Fixed moieties*<br>Moieties which are part of the drug in its active form | *Disposable moieties*<br>Moieties which have to be disjuncted to get the drug free in its active form |

of a bioactive compound by changing the moiety particularly involved, without essential interference with its other biological characteristics. It takes account of the multiconditionality of biological activity under the assumption that the requirements for the various steps or part-processes in the action may be fulfilled to a certain degree independently by different moieties in the drug molecule.*

The various biofunctional moieties in a biologically active compound cannot be considered to be fully independent. Therefore drug design is not simply the conjunction of various moieties potentially contributing to the wanted activity. The emphasis laid on particular aspects of drug action in relation to particular structural aspects can contribute, nevertheless, to a rational approach in the development of drugs. In the following sections various types of biofunctional moieties which play a role in pharmacokinetics, will be discussed.

Efforts to modulate pharmacokinetics and therewith the physiological availability of bioactive compounds can have as a purpose: (1) modulation of the distribution of the compound over the various compartments, e.g., to obtain a decrease in toxicity and a higher selectivity in action; and (2) modulation of the time–concentration relationship in the various compartments to obtain particular time–response relationships.

## A. Biofunctional Moieties Involved in the Partition of Drugs over the Various Compartments

Certain moieties in a drug molecule have a predominant influence on the distribution over the various compartments. They are called *conducting moieties* (*11*, *13*, *14*, *17*). In the case of transport by free diffusion the moieties governing the lipo-/hydrophility play a predominant role in distribution, since the compartments as a rule are separated by relatively lipid-rich barriers (the membranes) and also the compartments as such differ in lipo-/hydrophility. Highly hydrophilic, especially ionized groups in a drug will limit its rate of penetration through the biological membranes and thus restrict its distribution. They are called *restricting moieties*. Extreme lipophility of the drug too will limit its transport through the hydrophilic compartments and therefore restrict distribution. Moieties which confer to the drug a balanced lipo-/hydrophility will facilitate its penetration and its distribution. They are called *facilitating moieties*. If active transport processes are involved, selective

* The term drug molecule is used in this chapter in a broad sense, such that not only drugs, i.e., therapeutics, but also bioactive compounds in general are indicated, including toxons and biocides (*17*).

accumulation may take place. Particular chemical moieties in the drug molecule are required by the active transport system. These are called *selecting moieties.*

The various moieties mentioned may be part of the drug in its active form and are called *fixed moieties* or they may be only temporarily a part of the drug molecule being disjuncted under formation of the active compound (*98*), and are called *disposable moieties* then. As a rule in the disposable moieties there will be a larger degree of freedom with regard to molecular manipulation

TABLE IIA

CONDUCTING MOIETIES

(Moieties influencing the distribution of the drug in its active form over the various compartments)

| *Restricting moieties* | *Facilitating moieties* | *Selecting moieties* |
|---|---|---|
| Fixed or disposable, conferring to the drug extreme hydrophility or extreme lipophility, restricting its transport and distribution | Fixed or disposable, conferring to the drug a balanced lipo-/hydrophility, making it suitable for easy penetration into hydrophilic and lipophilic compartments, thus facilitating distribution | Fixed or disposable, adapting the chemical properties of the drug to the active transport mechanisms such that based on active transport selective accumulation in certain compartments takes place |

| *Selective bioactivation* | *Selective bioinactivation* |
|---|---|
| Introduction of vulnerable moieties may result in a selective bioactivation in the target tissue or target compartment and thus increase the therapeutic index and a selectivity in the action | Introduction of vulnerable moieties may result in a selective bioinactivation outside the target tissue or target compartment, and thus increase the therapeutic index and selectivity in the action |

than in the fixed moieties which are part of the drug in its active form and therefore must fit to the sites of action or at least may not disturb drug–receptor interaction.

Introduction into a drug molecule of groups subject to enzymic attack, called *vulnerable moieties*, may result in a *selective bioinactivation* or in a *selective bioactivation* in those compartments which are rich in the enzyme concerned. Molecular manipulation by introduction of the biofunctional moieties indicated opens a possibility for modulation of drug distribution over the various compartments. Table IIA summarizes the various types of conducting moieties indicated (*11, 13, 14, 17*).

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