Pharmacokinetics and Pharmacodynamics

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For drugs to produce significant effects, they must be able to interact with the body. This interaction is affected by a number of factors which include the properties of the drugs and mechanism by which drugs are absorbed through the body systems. In this article, the basics of pharmacokinetics and pharmacodynamics are discussed. Given emphasis are some of the factors affecting drug action, namely lipophilicity, acid sensitivity, and BBB penetration.

Pharmacokinetics

It is defined as the **study of the kinetics of drug absorption, distribution, excretion, and metabolism**. Pharmaceutical scientists study the pharmacokinetics of drugs to enhance the efficiency of drug delivery and, in the process, reduce the risk of toxicity to the patient during drug therapy. Different drugs tend to have different drug kinetics. There are also some drug delivery systems available that can enable pharmaceutical scientists to study different rates of drug release.

Pharmacodynamics

There is a direct correlation between drug concentration and its effect on patients. This relationship is studied by describing **pharmacodynamics** of drugs. Pharmacodynamics specifically refers to the relationship of drug concentration at the site of action and the

resulting effects. Also included in the study of pharmacodynamics are the time course and intensity of the therapeutic and adverse effects.

Drugs usually work by binding to a receptor and producing the desired effects. The concentration of drug present at the site of the receptor determines the intensity of the effect of the drug.

Other factors affecting the drug responses include the mechanism by which signal is transmitted into the cell by secondary messengers, some receptors present on the cell surface, and other regulatory factors that control gene translation and protein synthesis.

Drug Action

Drug action usually occurs in three phases:

- **Pharmaceutical phase**
- **Pharmacokinetic phase**
- **Pharmacodynamic phase**

The pharmaceutical phase includes the disintegration of the active substance in the drug. After the pharmaceutical phase, the pharmacokinetic phase proceeds which involve the distribution, absorption, metabolism, and excretion of the drug. When the drug forms an interaction with the receptor, the pharmacodynamics phase occurs where the biological effects are observed after the drug-receptor interaction.

For a drug to be considered effective, the drug must be **readily absorbable** in sufficient quantity. If the drug cannot be absorbed readily by tissues, no drug effect will happen. The drug should also **be easy to distribute** to the target tissues. Drugs should be able to attach themselves to target tissues to lessen its unnecessary effects to other tissues. The last important characteristic of a good drug is that it is **not metabolized very quickly**. This is an important factor so that it can maximize its effect on the target tissues.

Overview: principle phases in drug action

Classification	Pharmaceutical Phase	Pharmacokinetic Phase	Pharmacodynamic Phase
Process taking place	Disintegration of dosage form Dissolution of active substances	Absorption Distribution Metabolism Excretion	Drug-receptor (or enzyme) interaction in target tissue
Objective	Optimisation of pharmaceutical availability (drug available for absorption)	Optimisation of biological availability (drug available for action)	Optimisation of required biological effect (induction of therapeutic effect)

Factors Affecting Drug Absorption

The rate of absorption of the drug is affected by some factors. These factors include lipophilicity, solubility, ionization, degradation, metabolism and physiology. Three factors affecting the drug absorption are given focus, namely lipophilicity, acid sensitivity, and BBB (blood-brain barrier) penetration.

Lipophilicity

In general, the higher the lipophilicity of a drug, the higher its membrane permeability and the higher its metabolic clearance (first-pass effect).
Therefore, it is important to balance lipophilicity with metabolic susceptibility.
Drugs are sometimes modified to alter the properties of drugs. To make the drugs more lipophilic, the polar groups in the drug molecules should be masked. For example, the alcohol (-OH) groups of phenolic and alcoholic drugs can be converted to less polar esters or ether groups. These specific alterations are sometimes unwanted as these polar groups may have special interactions also with the receptors. In cases like this, prodrugs that can temporarily mask the polar groups may be employed.

In some instances also, the inclusion of polar groups in the drug structure may be important. This is mostly the case when the drug is too lipophilic that may inhibit drug-receptor interactions.

Acid Sensitivity

Some drugs undergo structural transformations in the presence of acids. These structural transformations greatly affect the therapeutic actions of drugs. For example, penicillin undergoes internal transformations forming esters. These esters are highly sensitive to the presence of acid in the stomach undergoing in the process hydrolysis reaction. Because of this, even before absorption in the gastrointestinal tract, the esters are already hydrolyzed affecting the drug action.

Because of this, there is a need to incorporate an electron-withdrawing group to reduce nucleophilicity of the compound, making it less susceptible to acid hydrolysis. Incorporating a benzene ring in the sides of the penicillin can make the penicillin compound less sensitive to acids, increasing the possibility of drug action.

BBB Penetration

Membrane Barriers: Blood-Brain Barrier (BBB) – layer of tightly packed endothelial cells that allow only small (< 500 Da) lipophilic drugs to cross by diffusion.
In the late 1900s, Paul Ehrlich demonstrated the existence of **Blood-Brain Barrier** by injecting aniline dyes into the blood of experimental animals. He was able to observe that all of the organs of the animals were stained by the dye, except the brain.

It was later then discovered that the central nervous compartments contain layers of tightly packed endothelial cells that can only allow small lipophilic drugs to cross by diffusion. The barrier consists of at least one lipid membrane that can accommodate hydrophilic molecules to enter into the extracellular spaces of the brain.

The drug molecules should be able to penetrate the blood-brain barrier for drug action to occur.

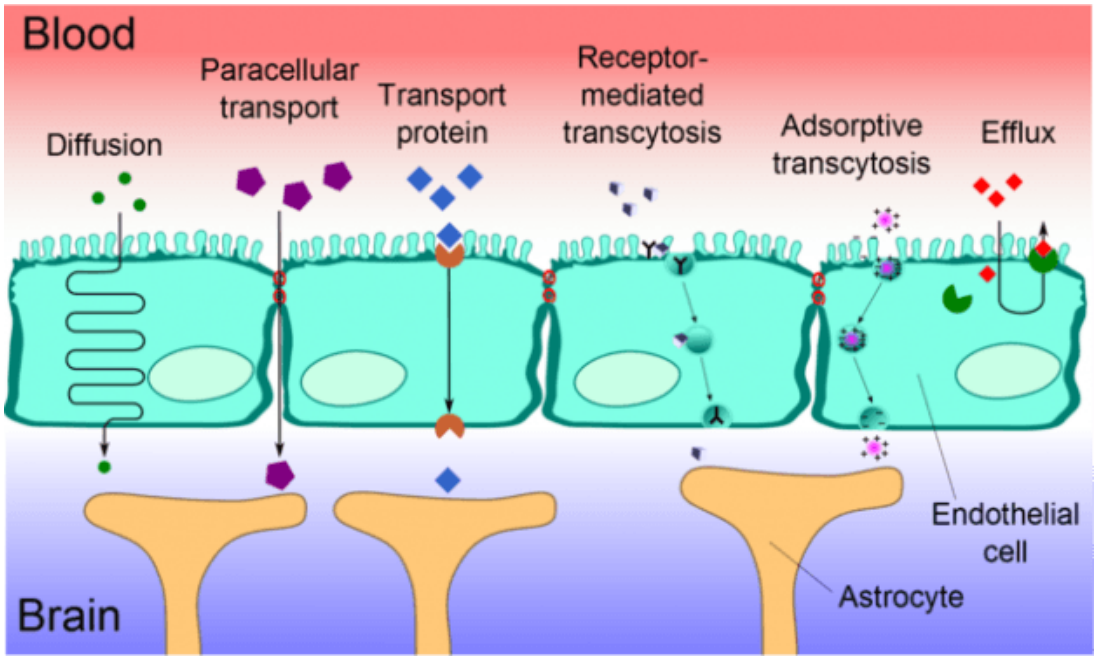

Image: “Schematic sketch showing the transport types at the blood-brain barrier.” by Kuebi= Armin Kübelbeck.
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Example: Morphine, a very strong analgesic, has only small penetrating ability into the blood brain barrier because of the presence of the two OH groups in its structure. Masking these OH groups with non-polar groups increases the lipophilicity of the drug, thereby increasing its penetrating ability.

Compared to morphine, the structure of **codeine** includes a methyl group attached to the hydroxyl oxygen. Since the addition of an alkyl group decreased the polarity of the original OH group in morphine, codeine has ten times more penetrating ability compared to morphine. Higher is the effect of esterifying the –OH groups of morphine with acetate groups in a diamorphine molecule. Since both OH groups are masked in the process, the molecule becomes more lipophilic and eventually increased BBB penetration by 100 times.

References

Nau, R., Sörgel, F., & Eiffert, H. (2010). Penetration of Drugs through the Blood-Cerebrospinal Fluid/Blood-Brain Barrier for Treatment of Central Nervous System Infections. Clinical Microbiology Reviews, 23(4), 858–883.

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