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Interacciones medicamentosas
Nuevas tendencias en psicofarmacología
Recientes progresos en el tratamiento de las enfermedades por virus

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INTRODUCTION

A single drug may cause various pharmacological effects which are generated by means of a reaction of drug molecules with the same type of receptors but also as a result of interaction with different types of receptors. For instance, alpha-sympathomimetic drugs induce vasoconstriction by reaction with adrenergic receptors located at the functional areas in vascular smooth muscle, but they also cause mydriasis by reaction with similar receptors in the M. dilator pupillae. On the other hand cyproheptadine blocks the actions of histamine and 5-hydroxytryptamine as a result of interaction with both types of receptors.

1. Drug-receptor interaction of a single compound

Most drugs not only produce more than a particular pharmacological effect, but a particular response is produced by a chain of events.

a. After injection of a drug or after swallowing a medicament, absorption into the bloodstream takes place, followed by distribution and elimination.
b. As a result of distribution a certain drug-concentration occurs at the level of the receptors.
c. Depending on the affinity towards the receptors and the concentration of the drug near the receptors a certain degree of receptor-occupation takes place.
d. Receptor-occupation may lead to the generation of a stimulus (e.g. change in membrane potential) depending on the intrinsic activity of the drug.
e. The stimulus in turn induces the effect. This stimulus-effect relationship may be very complex (thresholds and receptor reserve may be present).

Especially in the intact situation, as is the case when medicaments are given to patients or drugs are studied in free moving or anaesthetized animals, the effect is always a very complicated function of the dose administered. Furthermore, the concentration at the level of the receptors does not remain constant in time (pharmacokinetics).

It is obvious that an analysis at the receptor level will be most successful in the simplest possible situation. These are the isolated organs, individual neu-
Drug interaction at the receptor level

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In vitro it may be possible to obtain a consistent dose response relationship. In many cases for agonistic drugs S-shaped log dose-effect curves may be found.

2. Drug-interaction

The combination of a drug with a second drug may lead to a variety of interactions.

a. Antagonism: The effect of a drug may be reduced by the second drug. There are many causes of drug antagonism.
b. Synergism: The effect of a drug may be augmented by the second drug. Again there are many ways of drug interaction resulting in synergism.

In the clinical situation many forms of drug-interaction may be encountered. Due to the various components in the action of a single drug and the various active metabolites that may be formed from the drug administered, the interaction with a second drug may be very complex. Even the effect of a single drug may be the result of an interaction with endogenous compounds and/or with active metabolites formed in the body. Drug-interaction may be most simply be analyzed from a study of the change in the dose response curve produced by the second drug.

3. Drug-interaction at the receptor level

Also here drug-interaction may result in synergism or antagonism. If the second drug diminishes the response of the agonist in some way, one speaks of antagonism or desensitization. If the second drug augments the effect of the agonist in some way, one speaks of synergism or sensitization.

Depending on the dose administered, the interaction of a given combination of two drugs may result in synergism at a certain dose and in antagonism at an other dose (also called dualistic interaction). At the level of the receptors the following possibilities may occur:

1. Chemical interaction (antagonism or synergism).

The interacting drug may bind to the agonistic drug thereby diminishing the concentration of the agonist in the environment of the receptors, e.g. EDTA sequesters Ca++ or germanine sequesters curare.

2. Competitive interaction (antagonism, dualism or synergism).

If two or more drugs react with the same receptors, these drugs may compete with each other for occupying receptors. Depending on the intrinsic activity of the various drugs the interaction results in antagonism or synergism. Antagonism occurs if one drug has a high and the other a low intrinsic activity. In case of synergism both drugs have intrinsic activity and are therefore both agonists. A drug that is inactive by itself can never produce competitive synergism.

A classical example of competitive antagonism is the combined action of curare and acetylcholine. The log dose-response curves shifts to the right. It must be realized that when atropine alone is administered to a patient, interaction
with endogenous acetylcholine occurs (competitive antagonism). Pilocarpine, a partial agonistic muscarinic drug, also interacts with endogenous acetylcholine resulting in synergism or antagonism depending on the level of acetylcholine present in the tissue.

3. Allosteric interaction.

For competition it is not strictly necessary that the two drugs react with identical receptors. The same phenomenon occurs in case of allosteric interaction that is the two drugs react with different receptors but the two drugs either facilitate or impair each other with respect to interaction with their proper receptors. In this case an inactive drug may cause a shift of the curves to the right (antagonism) or a shift to the left (synergism or sensitization).

4. Non-competitive interaction.

A drug may influence the response of an agonistic drug by reaction with other receptors and consequently by modifying the chain of events leading from receptor occupation by the agonist to the ultimate response of the agonist. The non-competitive antagonist may modify the stimulus generation by the agonist in a positive or negative way (synergism or antagonism) or modify the relationship between stimulus and effect and thereby increasing or decreasing the number of spare receptors.

A classical example of a non-competitive antagonist is papaverine (histamine or acetylcholine as agonist). Obviously there may be a large variety of all kinds of non-competitive antagonists and synergists.

5. Functional interaction.

In this case two drugs react with their receptors proper leading for both to the generation of two different stimuli. For instance, one drug may cause an EPSP and the other an IPSP on the same type of neurons, so that a kind of antagonism occurs that is analogous to competitive interaction. A classical example is the interaction between mecholyl and isoprenaline with respect to the tonus of the tracheal muscle.

CONCLUSION

The various forms of drug-interaction at the level of the receptors will be discussed on basis of the change in the dose-response curve they may show. The importance for the clinical situation will be stressed as far as possible.