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Modeling of the Underlying Chemistry of the Ligand-receptor Interactions

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One of the topical problems both of biochemistry and pharmacology is the unraveling the mechanisms of the action of the drugs. The present research attempts to model one of the key steps of the action of drugs, namely the processes underlying the interaction of the drug with corresponding receptor. The modeling is intended to clarify the role of chemical reactions in the process of the formation and decay of the ligand-receptor complexes.

The modeling is based upon the hypothesis that ligand-receptor interaction (binding) could involve the chemical reactions between the preparation and amino acid residues forming the binding centers of many receptors. The affinity between the drug and receptor is the prerequisite to initiate the reaction, and since the existing preparations represent a wide variety of different classes, the model should include rather simple and universal process. It was suggested that this process involves single electron transfer. Since the binding also should be reversible, we assume that it results in the chemical transformation of the paramagnetic form of the preparation leading the decay of drug-receptor complex.

The present research models the interactions of nifedipine (**I**) with Ca^{2+}-receptor and lappaconitine (**II**) with Na^{+} channel. The possibility of single electron transfer between **I**, **II** and the corresponding amino acids has been studied in solution under the photoinitiation of the process. The use the photoinitiation to model the single electron transfer, as well as the investigations of the reactions with amino acids in solution is based on the assumption that the properties of the paramagnetic species formed is independent of the way of their generation.

In the case of nifedipine and lappaconitine, the above hypothesis was experimentally confirmed by explorations of chemically induced dynamic nuclear polarization (CIDNP) effects. The radical anion of nifedipine resulting from the photoinduced electron transfer between nifedipine and tyrosine is unstable and converts to nitrosopyridine within the microsecond time scale. Molecular modeling shows that the latter is incapable to bind to receptor.

In the case of **II**, according to pharmacological studies the therapeutic effect is thought to be due to the irreversible blocking of Na^{+}-channels (reference data points to binding to the site 2 of the channel with known sequence of amino acids). In the investigations of the model photoinitiated interaction of the lappaconitine with tyrosine and tryptophane in solution by means of CIDNP techniques, including time-resolved version, it has been found that the resulting radical anion of **II**, similar to nifedipine radical anion, is unstable and transforms into the compounds that does not reveal therapeutic activity.

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