Exploring non-covalent interactions between drug-like molecules and the protein acetylcholinesterase

Lotta Berg

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Fakultetsopponent: Professor, Joel L. Sussman,
Department of Structural Biology, Weizmann Institute of Science,
Rehovot, Israel

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Author
Lotta Berg

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Abstract
The majority of drugs are small organic molecules, so-called ligands, that influence biochemical processes by interacting with proteins. The understanding of how and why they interact and form complexes is therefore a key component for elucidating the mechanism of action of drugs. The research presented in this thesis is based on studies of acetylcholinesterase (AChE). AChE is an essential enzyme with the important function of terminating neurotransmission at cholinergic synapses. AChE is also the target of a range of biologically active molecules including drugs, pesticides, and poisons. Due to the molecular and the functional characteristics of the enzyme, it offers both challenges and possibilities for investigating protein-ligand interactions. In the thesis, complexes between AChE and drug-like ligands have been studied in detail by a combination of experimental techniques and theoretical methods. The studies provided insight into the non-covalent interactions formed between AChE and ligands, where non-classical CH···Y hydrogen bonds (Y = O or arene) were found to be common and important. The non-classical hydrogen bonds were characterized by density functional theory calculations that revealed features that may provide unexplored possibilities in for example structure-based design. Moreover, the study of two enantiomeric inhibitors of AChE provided important insight into the structural basis of enthalpy-entropy compensation. As part of the research, available computational methods have been evaluated and new approaches have been developed. This resulted in a methodology that allowed detailed analysis of the AChE-ligand complexes. Moreover, the methodology also proved to be a useful tool in the refinement of X-ray crystallographic data. This was demonstrated by the determination of a prereaction conformation of the complex between the nerve-agent antidote HI-6 and AChE inhibited by the nerve agent sarin. The structure of the ternary complex constitutes an important contribution of relevance for the design of new and improved drugs for treatment of nerve-agent poisoning. The research presented in the thesis has contributed to the knowledge of AChE and also has implications for drug discovery and the understanding of biochemical processes in general.

Keywords
acetylcholinesterase, drug discovery, density functional theory, hydrogen bond, nerve-agent antidote, non-covalent interaction, protein-ligand complex, structure-based design, thermodynamics, X-ray crystallography

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