Modeling of structure of gamma-aminobutyric acid transporters as an essential biological and therapeutic target

In the long and arduous process of finding new drugs computer modeling methods play an important role. The study of interactions between bioactive compounds and macromolecules can be carried out using methods based on the structure of a biological target or constructing appropriate models. In the presented project, the molecular targets for research are transporters of gamma-aminobutyric acid (GABA). Gamma-aminobutyric acid is a major mediator of the nervous system responsible for the inhibition of various processes. After release from nerve cells and taking of the effect it is eliminated in two ways: reuptake or metabolism. GABA transporters are responsible for its reuptake, and their structure has not been known so far.

Dysfunction of nerve cells releasing gamma-aminobutyric acid can lead to a variety of pathological phenomena and the occurrence of diseases such as anxiety disorders, epilepsy, neurodegenerative disorders, schizophrenia, insomnia, motion impairment or pain states. Ability to potentiate the GABA activity by inhibiting its reuptake is an attractive therapeutic target. The first drug of this group introduced on the market and so far only is tiagabine which is used in the treatment of epilepsy. There are ongoing studies on the use of the compounds blocking GABA transporters in the therapy of disorders other than epilepsy, *i.e.* in the treatment of anxiety, depression and pain.

The scientific goal of the project is to build new models of transporters for gamma-aminobutyric acid (GAT-1, GAT-2, GAT-3 and GAT4) and to examine their interactions with known potent substances, including drug tiagabine.

These transporters will be built based on the structure of other transporting proteins, *i.e.* dopamine and serotonin transporters. The obtained models will be evaluated in terms of molecular structure, and the best ones will be used to investigate the binding mode of selected compounds. The reasons why certain substances block all GABA transporters, and other substances affect only the selected types of transporters will be determined. This information may be used in the future for the design of novel compounds having the desired effect on various types of GABA transporters.

Due to the project the more detailed structure of the transporters for gamma-aminobutyric acid will be known. Models of four mouse transporters GAT-1, GAT-2, GAT-3 and GAT-4, the most commonly used in biological tests and their human counterparts (GAT-1, BGT-1, GAT-2 and GAT-3) will be built. Conducted analysis will demonstrate both interspecies differences as well as differences between different types of transporters. Presented project raises issues that have not been previously explored. This ensures the publication of results in renowned international journals. The project will contribute to a better understanding of gamma-aminobutyric acid transporters and will provide an important base for research groups looking for new inhibitors of these targets with potential application in the treatment of epilepsy, depression, anxiety or pain.