COMPLEX INTERFERENCE MECHANISMS IN THE NICOTINIC PATHOGENY OF NEURODEGENERATIVE DISORDERS – CELLULAR AND SUBCELLULAR REGULATOR EFFECTS OF NATURAL COMPOUNDS GALANTAMINE AND GINKGOLIDE B.

Neuro-degenerative disorders (like Alzheimer disease) represent a major health problem. The available therapies are yet far from offering a cure, and can only slow down the disease's progression. Clinically significant results are obtained, so far, by increasing the available amount of acetylcholine in the central nervous system (by means of acetylcholinesterasic drugs), but the intimate mechanisms are not ellucidated yet. Recent research shows promising results in the case of two natural compounds: galantamine, an alkaloid from snowdrops, and ginkgolides, terpenoids from Ginkgo biloba. Galantamine shows a mild anti-cholinesterase action and is an allosterically potentiating ligand of nicotinic receptors. Both drugs show neuroprotective effects by incompletely understood mechanisms. Taking into account this general picture, our project is concerned with the mechanisms of interference of these drugs with the nicotinic pathogenic chains, on the level of membrane lipid bilayers and nicotinic receptors. We wish to approach two particular aspects on which, to our knowledge, there is no available information so far. Our first aim is directed to the interaction of galantamine and ginkgolide B with the cellular membranes, a phenomenon that might partially explain their neuroprotective effects. We intend to perform electrophysiological experiments on model membranes – lipid bilayers, by means of the Black Lipid Membranes (BLM) and Solid Supported Membranes (SSM) techniques. Our second goal is the patch-clamp study of the mechanisms of interference between the two selected drugs and the nicotinic receptors. We wish to focus our researches on the effects of galantamine and ginkgolide B on receptor desensitisation, on which there are no available data to the present time. The experimental data will be correlated and completed by theoretical models of the corresponding mechanisms of interaction.