

## **On the role of gangliosides, insulin and zinc ions in amylin interactions with biomimetic membranes**

Diabetes mellitus is a metabolic disease that currently affects more than 420 million people worldwide and the World Health Organization predicts that the number of deaths caused by diabetes will double by 2030. According to studies, about 90% of diabetic patients suffer from type II diabetes. It is characterized by the first manifestation of the disease in an adult life and its progress leads to death of pancreatic beta cells, which results in the impaired insulin secretion. Amylin, Islet Amyloid Polypeptide (IAPP) forms insoluble fibrillar deposits (amyloid) in the pancreas of patients suffering from type II diabetes mellitus. These deposits have been identified in over 90% of patients suffering from type II diabetes mellitus. The presence of amyloid is associated with the death of insulin-producing beta cells, which in turn contributes to the progress of the disease. The results of studies suggest that the action of amylin on biological membrane of beta cells is a cornerstone of amylin cytotoxicity. Still, little is known about the mechanisms governing amylin-induced destruction of the pancreatic cells.

The aim of this project is to investigate the mechanisms of action of pancreatic islet amyloid polypeptide, amylin, on model lipid membranes and to follow structural changes in both amylin and lipid layers that result from these interactions. Simple models of cell membranes will be used and their composition will resemble the lipid composition of beta cell membranes. For this purpose, gangliosides will be used. Gangliosides contain lipid and sugar moiety within the molecule, naturally occur in beta cell membranes and they are important in amyloid-membrane interactions. This way prepared biomimetic membranes will be subjected to amylin in order to determine:

- the structural changes of amylin upon interactions with lipid membrane;
- the effect of the peptide on the structural integrity and stability of the lipid membrane;
- the mechanisms that govern the process of amylin incorporation into the lipid membranes;
- to what extent amylin aggregation induces its cytotoxicity.

The influence of amylin on the lipid layers will also be examined in the presence of insulin and / or zinc ions. In natural systems, the amylin secretion is accompanied by insulin secretion (but the concentration of amylin is significantly lower than insulin), as well as a high concentration of zinc ions. So far, the conducted studies do not give definite information about the role of insulin and zinc ions in the pathological changes induced by amylin deposits. To verify their role in the amylin-lipid membrane interactions is one of the objectives of this project.

This project includes a comprehensive study of structural consequences of the cytotoxic process of amylin aggregation in type II diabetes and mechanisms of cell destruction by amyloidogenic peptides. The experiments planned within the project cover basic research and the results will contribute directly to acquiring new knowledge about the molecular mechanisms responsible for the development of not only type II diabetes mellitus but all amyloid diseases, including neurodegenerative disorders such as Alzheimer disease. This knowledge is a cornerstone in designing of new drugs and therapeutic strategies.