N-methyl-D-aspartate receptors (NMDAR) represent a subtype of ionotropic receptors of glutamate (Glu), the main excitatory neurotransmitter in the central nervous system (CNS). Apart from their direct participation in glutamatergic neurotransmission, NMDAR play key roles in brain development, plasticity, learning and memory. Their excessive activity contributes to the development of most common CNS diseases, including stroke and neurodegenerative diseases: Huntington disease, Parkinson disease and Alzheimer disease.

Almost all we know about NMDAR concerns those located in neurons. Recent studies provided evidence for the presence of NMDAR in astrocytes, the cells which in the CNS are an active partner of neurons in neurotransmission. However, little is known about the function of astrocytic NMDAR. Own preliminary results have shown that stimulation of NMDAR in astrocytes inhibits the expression and activity of glutamine synthetase (GS), an enzyme which catalyzes Glu synthesis and inactivation, and as such plays a direct role in the regulation of glutamatergic neurotransmission. The question arose what are the intracellular metabolic pathways that mediate GS regulation following NMDAR activation. The present project attempts at answering this question. Indirect evidence prompted to investigate two signaling pathways which are ubiquitously present in mammalian tissues: i) the phosphatidylinositol 3-kinase (PI3K)-Akt-Foxo pathway and ii) a pathway engaging cyclin-dependent kinase 5 (CdK5) associated with the nuclear factor (erythroid-derived 2)-like 2 (Nrf2). Studies will be carried out on cultured mouse astrocytes, which will be treated with NMDA and/or inhibitors of the individual components of the pathways. In case of Nrf2, its expression will also be blocked using silencing with small interfering RNA (siRNA). Studies will encompass analysis of mRNA and protein expression using real time PCR and Western Blot techniques, and of enzyme activity. Detailed analysis of the pathways will include measurements of the content and activity (degree of phosphorylation) of their protein constituents.

The newly acquired knowledge of the molecular mechanism(s) that translate activation of astrocytic NMDAR to the regulation of GS expression and activity is likely to reveal a novel aspect of astrocytic plasticity related to glutamatergic neurotransmission.