The hallmark of the mammalian brain is the ability of processing and storing information in synapses and highly organized neuronal networks. The brain can adapt and change in response to various events under physiological conditions (i.e. learning) and pathophysiological conditions (i.e. epilepsy, stroke). An underlying process is the plasticity of synaptic connections, most apparent in changes in the shape and efficacy of neurotransmission. Despite ongoing research on the mechanisms of synaptic plasticity, it's regulation is still poorly understood. Each synapse contains thousands of proteins that move around between place of synthesis and destination which could be on the synapse surface. Rate of protein trafficking is regulated by covalent and reversible attachment of fatty acids such as palmitate to the protein (called S-palmitoylation), turning it into more hydrophobic (fat like) what eventually makes the protein more prone to be incorporated into synaptic membrane. We have found that when rats learn to navigate in space or they explore new environment, the pattern of protein palmitoylation changes. We believe this reversible modification of synaptic proteins could be critical for learning, because when we blocked palmitoylation with biochemical 2-bromopalmitate, long-term potentiation of excitatory synaptic transmission has been significantly impaired. In the proposed project, we would like to investigate reciprocal interaction of dopamine and palmitoylation of synaptic proteins in the hippocampus- a brain structure critical for learning and memory. We plan to combine multiple biochemical methods enabling detection of protein lipid modifications (i.e. mass spectrometry) as well as genetically manipulate the activity of enzymes responsible for palmitoylation. We will perform behavioural tests on transgenic animals, in which activity of those enzymes is reduced. We plan to record electrical signals from synapses in single neurons and neuronal networks as wells as currents conducted by synaptic proteins in palmitoylated and non-palmitoylated states.

Taking advantage of various experimental models and advanced quantitative methods we will try to answer the following questions:

1) What is the role and time-course of palmitoylation in synaptic plasticity?
2) How does dopamine influence palmitoylation of synaptic proteins?
3) Which proteins undergo palmitoylation-dependent changes in function in learning and how is this process controlled?

Altogether, understanding the fundamental mechanisms of the plasticity of synaptic connections and neuronal network code lies in the center of contemporary neurobiology, neuropharmacology, and medicine. The results of this project will shed new light on the general mechanisms governing brain plasticity and may be also important for the understanding of dopamine role in brain physiology as well as planning new therapeutic strategies for the treatment of some neurological diseases associated with dysfunction in dopamine signaling.