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The complex functions of the cerebral cortex relay on neuronal networks of highly interconnected excitatory (glutamatergic) neurons and inhibitory (GABAergic, GABA: gamma aminobutyric acid) interneurons. In general, both excitatory and inhibitory neurons are responsible for transmitting and processing the information in the brain. Inhibitory neurons shape information processing as well as protect the brain against pathological overexcitation. Although inhibitory interneurons represent a minority of all cortical neurons (about 20%) their dense axonal arborization allows them to control the entire cortical network. There is a large diversity of cortical inhibitory neurons based on differences in morphology, intrinsic membrane properties, and connectivity, features of their input and output synapses as well as the expression of specific molecular markers. GABA, the main inhibitory neurotransmitter in the cortex, acts via different modes depending on the type of the receptors (fast – in order of few ms, slow – in order of few hundred ms and tonic). Therefore, determining the specific roles of different subtypes of inhibitory interneurons and different types of the inhibition is therefore fundamental to understand brain function.

The most amazing attribute of the brain is its ability to collect new information from the environment and store it in order to produce changes in behavior. This is a part of the process called plasticity. The scope of the project is to study learning and memory mechanisms in the cerebral cortex. Traditionally, changes in the excitatory transmission have been postulated to underlie learning and memory mechanisms. On the other hand, inhibition is also plastic. It has been suggested that learning-induced strengthening of inhibition is a way for preventing epileptiform activity. Alternatively, learning-induced strengthening inhibition is a way for increasing information precision. How learning changes activity of all the different subtypes of inhibitory interneurons has not yet been fully investigated. Moreover, the role of all the distinct subtypes of inhibitory neurons in the learning-dependent reorganization of cortical networks has not yet been completely understood.

The aim of the proposed project will be to answer the question, what the impact of learning-induced changes in inhibition mediated by two main inhibitory interneurons types is on the local excitatory network activity. The project will examine neurons expressing specific molecular markers: somatostatin-expressing (SOM) and parvalbumin-expressing (PV) neurons, which consist of 70% of all the inhibitory neurons in the cortex.

Using a simple mouse model of associative learning, our previous studies have found an increase both in excitability and in inhibition of excitatory neurons located in layer IV of the somatosensory cortex. After learning, the higher level of an enzyme producing GABA has been found in SOM but not PV neurons, which suggests that SOM neurons might be highly active during this learning paradigm. Moreover, more inhibitory synapses have been seen in electron microscopy analysis.

Electrophysiological recordings will be performed in single neurons (inhibitory or excitatory) in brain preparation and activity of different inhibitory subtypes will be controlled by optogenetic tools. Optogenetic tools, the newly high-edged technology, allow controlling the activity of distinct population of neurons by light-sensitive molecules (channelrhodopsin (ChR) or archaerhodopsin (Arch)), which can be expressed in a given neuronal type. ChR is a blue-light sensitive cation channel which photoactivation leads to the depolarization of the membrane potentials and the activation of a neuron. Arch is a green-light sensitive proton pomp which activation results in the hyperporarization of the membrane potential and suppression of the neuronal activity. Inhibition mediated by the entire population of a given inhibitory neurons subtype onto a single excitatory neuron will be evoked by photostimulation of channelrhodopsin expressed in this particular neuronal subtype (here, in SOM or PV neurons).

The results obtained within this project will provide a novel and essential contribution to the extensive scientific effort aiming at elucidating the mechanisms of learning and memory. Proposed study will add crucial information on the functional (physiological) level about the mechanisms of the plastic changes in two main inhibitory neurons in the cerebral cortex and the role of these changes in controlling of excitatory network in learning and memory. In the further, obtained data may contribute to the progress of biomedical sciences that study brain pathologies, since the disturbance in the balance between excitation and inhibition has been recognized in many pathological stages, such as e.g. epilepsy, depression, schizophrenia, autism spectrum disorder, and Alzheimer and Parkinson diseases.