ABSTRACT

Neurosteroids play an important role in the brain physiology and pathophysiology. They control inhibitory and excitatory neurotransmission. The presented thesis aims to investigate the biological significance of neuroactive steroid 3_5_-pregnanolone glutamate (3_5_P-Glu). We investigate the effect of 3_5_P-Glu in naïve rats. Next, we evaluate the effects of 3_5_P-Glu in animal model of schizophrenia and excitotoxic lesion of hippocampus induced by N-methyl-D-aspartate (NMDA). Furthermore, we morphologically characterize the NMDA lesion model. 3_5_P-Glu did not induce significant psychotomimetic side effects such as hyperlocomotion, sensorimotor grating deficit or memory impairment. Next, 3_5_P-Glu showed dose dependent pro-cognitive effects in animal model of schizophrenia; however, it had no effect on hyperlocomotion in this model. 3_5_P-Glu also ameliorated spatial learning deficit of rats induces by NMDA lesion of hippocampi in the Carousel maze and had mild effect on NMDA induced damage of hippocampus when applied before. Additionally, the morphological analysis of hippocampal NMDA lesion revealed overexpression of NMDA receptor NR1 and NR2B and downregulation of GABA$_A$ receptor _5 subunits. The lesion was very conservative, did not spread to other structures and did not affect GABAergic interneurons. Furthermore, the lesion progression was accompanied with severe activation of microglia and astrogliosis.

Taken together, this thesis shows that neuroactive steroid 3_5_P-Glu does not induce psychotomimetic side-effects typical for NMDA channel blockers. Moreover, results show that 3_5_P-Glu may represent a potential neuroprotective and procognitive drug.

Keywords: 3_5_-pregnanolone glutamate, NMDA lesion, animal model of schizophrenia GABA$_A$ receptor, NMDA receptor, neuroprotection.