ABSTRACT

Glutamatergic system is the main excitatory system and glutamatergic receptors are the most abundantly expressed in whole central nervous system. The most widespread type of glutamatergic receptors are N-methyl-D-aspartate (NMDA) receptors which are essential for physiological development of nervous tissue, synaptic plasticity and cognitive processes. On the other hand, over-activation of these receptors leads to excitotoxic damage of nervous tissue and serious neurological consequences for future quality of life. Disruption of glutamatergic system is common feature for hypoxic-ischemic damage, traumatic brain injury, neurodegenerative and neuropsychiatric diseases. Therefore glutamatergic system and specifically NMDA receptors are an attractive target for neuropharmacological research.

Presented thesis explores the effect of several molecules with modulating inhibiting effect on NMDA receptor. Work is preferentially focused on application research; the main aim is evaluated therapeutic potential of studied compounds. First group of compounds is represented by neuroactive steroids pregnanolone glutamate and pregnanolone hemipimelate, which are allosteric inhibitors of NMDA receptor. Here, their neuroprotective effect is demonstrated in hypoxic-ischemic and excitotoxic damage of nervous tissue. Second group of molecules explore tacrine and its 7-methoxyderivative (7-MEOTA). Apart from NMDA action these molecules have simultaneously inhibitory effect on acetylcholine esterase. Here we describe high efficiency of 7-MEOTA in animal model of excitotoxic damage of dorsal hippocampus. Importantly 7-MEOTA shows stronger neuroprotective effect compared to clinically used memantine. The last part of study is a research of rapid antidepressant effect of NMDA receptor antagonist ketamine in the model of major depressive disease. We describe an activation of mTOR signal pathway following administration of ketamine and its connection with stress reaction of organism.

Together, present thesis shows a putative role of glutamatergic system in animal models of excitotoxicity, hypoxic-ischemic damage and major depressive disorder. We proved utility of varied compounds in neuroprotection – all act via NMDA receptor. Tested agents demonstrated a promising neuroprotective potential to be explored in preclinical models of CNS diseases associated with glutamatergic system.

KEY WORDS: glutamatergic system, NMDA receptor, excitotoxicity, neuroactive steroid, tacrine, 7-MEOTA, ketamine, neuroprotective effect