ABSTRACT

In preclinical research on Alzheimer's disease pharmacotherapy, attention is paid to multipotent compounds, enabling intensification of the effect by targeting multiple pathophysiological mechanisms. The aim of the thesis was to assess the effect of multipotent compounds and combination therapy in models of cognitive deficit in the rat. The mechanism of action of the tested compounds was modulation of neurotransmitter systems. The aim of the first part of the study was to compare the effect of experimental monotherapy and combination therapy with an N-methyl-D-aspartate (NMDA) receptor antagonist and a γ-aminobutyric acid type A ($GABA_A$) receptor positive modulator in the trimethyltin-induced model. Superiority of the combination therapy was proven by histological analysis of hippocampal neurodegeneration; however, it did not reach statistical significance in the cognitive test. The other part of the thesis focused on multipotent tacrine derivatives. We demonstrated a positive effect of 6-chlorotacrine-6-nitrobenzothiazole hybrid, as well as 6-chlorotacrine-L-tryptophan hybrid, acting as acetylcholinesterase inhibitors, in the scopolamine-induced model of cognitive deficit. Besides, we demonstrated a low risk of serious side effects of other tacrine derivatives acting as NMDA receptor antagonists. This finding justifies initiation of preclinical efficacy studies. The positive results prompt further research on the effects of the tested compounds in Alzheimer's disease models.

Key words: acetylcholinesterase inhibitor, Alzheimer's disease, animal models, behavioral pharmacology, dementia, cognitive deficit, combination therapy, multipotent compounds, multi-target-directed ligands, NMDA receptor antagonist, tacrine.