Neuroactive steroids as neuroprotective agents

Neuroactive compounds are synthetic analogues of neurosteroids that are naturally synthesized in the nervous tissue from cholesterol or steroidal precursors from peripheral sources. The neuroprotective effect of neurosteroids or neuroactive steroids is supposed to be realized via rapid, non-genomic mechanism. Multiple studies have been already performed to demonstrate efficacy of neurosteroids in the treatment of various central and peripheral nervous system diseases (e.g. ischemia, seizures, neurodegeneration, etc.). However, the mechanisms of neuroprotective effect of neuroactive steroids remain unclear and accumulating evidence indicate that this process can be regulated in multi-target manner. Moreover, neuroprotection include mechanisms protecting against neuronal injury/damage or degeneration according to acute or chronic origin of pathological process. As such, research targeting design and development of neuroprotective steroids with therapeutic potential is extremely challenging. In the last decade, we have synthesized a library of neuroactive steroids that act as potent negative modulators of N-methyl-D-aspartate receptors (NMDARs) that play significant role in learning and memory. Also, we have shown that these compounds do exhibit strong neuroprotective effect in in vivo models. Currently, our main avenue of investigation is development of an in vitro multiplexed screening platform to identify molecules with strong neuroprotective effect. Therefore, we have developed a methodology for neuroprotective effect screening in the model of glutamate/NMDA-induced excitotoxicity on embryonic cortex neurons. We conclude that pretreatment with our neurosteroids significantly reduced acute NMDA/L-glutamic acid excitotoxicity mediated by Ca2+ entry and consequent ROS release and caspase-3 activation. Compounds 6 (IC50 = 5.8 µM), 7 (IC50 = 12.2 µM), 9 (IC50 = 7.8 µM), 13 (IC50 = 1.1 µM) and 16 (IC50 = 8.2 µM) attenuated glutamate-induced Ca2+ entry more effectively than memantine (IC50 = 18.9 µM). Moreover, compound 13 was more effective than MK-801 (IC50 = 1.2 µM). This drop in Ca2+ level resulted in corresponding reactive oxygen species suppression and prevented glutamate-induced caspase-3 activation.

Biography

Eva Kudova has been working at Institute of Organic Chemistry and Biochemistry in Prague, Czech Academy of Sciences (IOCB) since 2002. She completed her PhD in 2009 at Charles University in Prague. Then, she spent two years in the lab of Douglas F Covey, Washington University School of Medicine in St. Louis, Missouri, USA. Her research interest includes Steroidal Chemistry. She has been working in the field of Steroidal Chemistry for more than 10 years. Her major avenue of investigation is “Design and synthesis of new neuroactive steroidal compounds and structure-activity relationship studies affording NMDARs ligands”. Also, she and her colleagues have proposed screening pipeline that should serve as a screening platform for neuroactive steroids targeting CNS diseases and showing neurosteroids’ drug-likeness.

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