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Steroidal molecules as rapid acting therapeutics: Promises and pitfalls

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Neurosteroids are endogenous steroids that are synthesized and act in the central nervous system from cholesterol. Neurosteroids produce rapid effects on neuronal excitability and synaptic function that involve direct or indirect modulation of neurotransmitter-gated ion channels, or other neurotransmitter receptors and transporters, rather than classic, nuclear hormone receptors. The central effects of these compounds are mediated by interactions with ligand-gated ion channels such as glutamate, GABAA, glycine and nicotinic acetylcholine receptors. N-Methyl-D-aspartate receptors (NMDARs) are glutamate gated, calcium-permeable ion channels that are activated during excitatory synaptic transmission and are implicated in various forms of synaptic plasticity, which underlies learning and memory processes. Several allosteric modulators, including neurosteroids, can influence the activity of NMDARs. To find novel potentially beneficial drugs to treat neurological damage/neurodegeneration is one of the most investigated areas in contemporary pharmacology and neuroscience. Therefore, we design, synthesize and screen SMART steroids – Steroidal Molecules as Rapid-acting Therapeutics. SMART steroids are neuroactive molecules, targeting primarily the NMDA receptors and show neuroprotective properties and minimal side effects in animal models. A broad variety central nervous system diseases (neurodegeneration, ischemia, traumatic brain injury, etc.) have been associated with glutamate induced excitotoxicity under pathological conditions, a specific form of neuronal cell death caused by overactivation of NMDARs. Our research demonstrate that the inhibitory effect of SMART steroids on NMDA receptors has a neuroprotective effect, in both *in vitro* and *in vivo* models of neurodegeneration, thereby indicating its potential therapeutic use. Additionally, positive allosteric modulators that increase the activity of NMDARs may provide a therapeutic aid for patients suffering from neuropsychiatric disorders where NMDARs hypofunction is thought to be involved, such as intellectual disability, autism spectrum disorder, or schizophrenia. Our results indicate that SMART steroids may be beneficial in treatment of several neurological diseases like epilepsy, neuropathic pain, AD, PD and others.

Recent Publications:

1. Vyklicky V et al. (2018) Surface expression, function, and pharmacology of disease-associated mutations in the membrane domain of the human GluN2B subunit. Front. Mol. Neurosci. 11:110.
2. Krausova B et al. (2018) Positive modulators of the N-Methyl- D-Aspartate receptor: structure-activity relationship study on Steroidal 3-Hemiesters. J. Med. Chem. 61(10):4505-4516.
3. Riedlová K et al. (2017) Distributions of therapeutically promising steroids in cellular membranes. Chem. Phys. Lipids. 203:78-86.
4. Vyklicky V et al. (2016) Preferential inhibition of tonically over phasically activated NMDA receptors by pregnane derivatives. J. Neurosci. 36(7):2161-2175.
5. Vyklicky V (2015) Block of NMDA receptor channels by endogenous neurosteroids: implications for the agonist induced conformational states of the channel vestibule. Sci. Rep. 5:10935.

Biography

Eva Kudova pursued her PhD (2009) from Charles University, Prague, Czech Republic. She has spent 2 years in the Lab of Douglas F Covey at the Washington University School of Medicine St. Louis, Missouri, USA. She worked as the Principal Investigator of the Neuroprotectives Targeted Research Group at the Institute of Organic Chemistry and Biochemistry (IOCB) of Academy of Sciences of Czech Republic, Prague. Currently, she is the Targeted Research Group Leader Assistant of the group Steroidal Inhibitors at IOCB leading the project "Neuroprotective Steroids".

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