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## Current insight into the neurosteroids effect on function of NMDA receptors

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**N**-Methyl-D-aspartate (NMDA) receptors (NMDARs) are a major class of excitatory neurotransmitter receptors in the central nervous system. They form glutamate-gated ion channels that are highly permeable to calcium and mediate activity-dependent synaptic plasticity. NMDAR dysfunction is implicated in multiple brain disorders, including stroke, various forms of neurodegeneration, chronic pain and schizophrenia. NMDARs are activated by agonists-glutamate and glycine, and their activity is modulated by allosteric modulators including endogenous neurosteroids pregnenolone sulfate and 20-oxo-5 $\beta$ -pregnan-3 $\alpha$ -yl sulfate (PAS) and their synthetic analogues. Our recent research allowed us to identify the site of action of PAS- the extracellular vestibule of the activated/desensitized receptor's ion channel pore. The structure of the open channel and recognition of molecular steps in the transition from closed to the open state provide a unique opportunity for the design of new therapeutic, neurosteroid-based ligands to treat diseases associated with dysfunction of glutamate system. As such, a series of pregnenolone analogues was prepared and these derivatives substituted with a carboxylic acid moiety at the end of an aliphatic chain of varying length at C-3, have the difference in potency between tonic and phasic inhibition increased with the length of the residue. Moreover, pregnenolone hemipimelate (PA-hPim), had no effect on phasically activated receptors while inhibiting tonically activated receptors. In behavioral tests, PA-hPim showed neuroprotective activity without psychotomimetic symptoms.

### Biography

Chodounska Hana has completed her PhD in 1983 from Charles University in Prague. She has been working at the Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic in Prague from 1986. During this period, she was the PI of steroidal research group for almost 10 years. She is author or co-author of 52 articles, 7 patents and has many contributions to scientific conferences. She has been Supervisor of undergraduate, graduate and doctoral students and the Lecturer of the course "Chemistry of Natural Products" at the Charles University and various scientific and popularizing lectures.

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