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Block of NMDA receptor channels by endogenous neurosteroids: Implications for synaptic transmission

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N-methyl-D-aspartate receptors (NMDARs) are ligand-gated ion channels permeable to calcium that play important roles in synaptic plasticity, learning, and memory. However, abnormal activation of NMDARs is thought to mediate neuronal degeneration. NMDARs can be allosterically modulated by numerous compounds including endogenous neurosteroid pregnanolone sulfate (PAS). Our results show that the onset of PAS inhibition is use-dependent, requiring receptor activation by both glutamate and glycine. The recovery from inhibition is use-independent; however, it is slowed by prolonged steroid application and accelerated by cyclodextrins. In search for amino acid residues involved in the steroid action we have mutated TM1 and TM3 membrane domains of NR1 and NR2B subunits (~50 mutations) and identified 2 residues which, when mutated to alanine, reduced steroid potency (particularly the threonine in the SYTAN motif of NR1 localized in the ion channel vestibule). Based on experimental results, molecular dynamics, and docking we propose a model of inhibitory action of steroids at NMDARs. Using newly synthesized PAS analogues we show that these steroids have a higher potency to inhibit tonically activated NMDA receptors than those synaptically activated (with up to a 10-fold difference in the IC_{50}). Behavioral experiments indicated neuroprotective activity of synthetic steroids in the absence of psychoactive like symptoms (that are typical for other NMDAR antagonists).Our results provide a unique opportunity for the development of new therapeutic neurosteroids based ligands to treat diseases associated with dysfunction of glutamate system.

Biography

Ladislav Vyklický received his MD degree from Charles University, Prague and a PhD in physiology and pathophysiology from the Institute of Physiology ASCR. His Postdoctoral work was as a Fogarty Visiting Fellow and Fogarty Visiting Scientist in the Laboratory of Developmental Neurobiology, National Institutes of Health, Bethesda, Maryland, USA (with Mark L. Mayer) and as a Visiting Scientist at the Max-Planck InstitutfürZellphysiologie, Heidelberg, Germany (with Professor Bert Sakmann). He was awarded numerous local and international grants including that from Howard Hughes Medical Institute. Currently he is the head of the Laboratory of Cellular Neurophysiology at the Institute of Physiology ASCR.

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