
МАТЕРИАЛЫ КОНФЕРЕНЦИИ
И ШКОЛЫ

**SIGMA 1 RECEPTOR – BIOLOGICAL FUNCTIONS AND ROLE
IN NEURODEGENERATIVE DISORDERS**

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Objectives. Sigma-1 receptor (S1R) is an endoplasmic reticulum resident transmembrane protein and changes in its expression or sequence are associated with neurodegenerative phenotypes. We studied S1R's cellular functions, intracellular localization and neuroprotective properties of S1R agonists that prevent synaptic loss in medium spiny neurons (MSNs) in Huntington's disease (HD) and mushroom "memory" spine loss in hippocampal neurons in Alzheimer's disease (AD).

Methods. Recombinant S1R protein was expressed and purified in baculovirus expression system. Giant unilamellar liposomes (GUVs) and supported bilayers were prepared from S1R-containing proteoliposomes. Neuronal cultures were prepared from WT, YAC128, presenilin-1-M146V-knock in (PS1-KI) and APP-KI pups. To visualize spine morphology, anti-DARPP32 immunostaining or TdTomato transfection were used. To study S1R's functions, we used calcium imaging and biochemical analyses. Mushroom spines were analyzed *in vivo* via transgenic GFP mice.

Results. We studied S1R localization to mitochondrial-associated membrane domains and biophysical determinants of S1R localization. We identified protein motifs responsible for S1R-cholesterol interactions that are essential for proper S1R targeting to the MAM regions. Knockdown or knockout of S1R expression impaired spine stability. S1R agonists 3-PPP and pridopidine prevented the loss of spines in YAC128 MSNs and the loss of mushroom spines in PS1-KI and APP-KI hippocampal neurons. S1R agonists also normalized calcium-signaling abnormalities observed in YAC128, PS1-KI and APP-KI neurons. Daily treatment of PS1-KI-GFP mice 30 mg/kg pridopidine daily prevented hippocampal mushroom spine loss *in vivo*.

Conclusions. S1R binds cholesterol directly and functions as a lipid raft-stabilizing protein of the ER. S1R agonist Pridopidine exerts synaptoprotective effects in preclinical models of HD and AD, suggesting that it has a therapeutic potential.

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