Calcium Release Mediated by Redox-Sensitive RyR2 Channels Has a Central Role in Hippocampal Structural Plasticity and Spatial Memory

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Resumen

Aims: Previous studies indicate that hippocampal synaptic plasticity and spatial memory processes entail calcium release from intracellular stores mediated by ryanodine receptor (RyR) channels. In particular, RyR-mediated Ca2+ release is central for the dendritic spine remodeling induced by brain-derived neurotrophic factor (BDNF), a neurotrophin that stimulates complex signaling pathways leading to memory-associated protein synthesis and structural plasticity. To examine if upregulation of ryanodine receptor type-2 (RyR2) channels and the spine remodeling induced by BDNF entail reactive oxygen species (ROS) generation, and to test if RyR2 downregulation affects BDNF-induced spine remodeling and spatial memory.

Results: Downregulation of RyR2 expression (short hairpin RNA [shRNA]) in primary hippocampal neurons, or inhibition of nitric oxide synthase (NOS) or NADPH oxidase, prevented agonist-mediated RyR-mediated Ca2+ release, whereas BDNF promoted cytoplasmic ROS generation. RyR2 downregulation or inhibitors of N-methyl-d-aspartate (NMDA) receptors, or NOS or of NADPH oxidase type-2 (NOX2) prevented RyR2 upregulation and the spine remodeling induced by BDNF, as did incubation with the antioxidant agent N-acetyl l-cysteine. In addition, intrahippocampal injection of RyR2-directed antisense oligodeoxynucleotides, which caused significant RyR2 downregulation, caused conspicuous defects in a memorized spatial memory task.

Innovation: The present novel results emphasize the key role of redox-sensitive Ca2+ release mediated by RyR2 channels for hippocampal structural plasticity and spatial memory.

Conclusion: Based on these combined results, we propose (i) that BDNF-induced RyR2-

mediated Ca2+ release and ROS generation via NOS/NOX2 are strictly required for the dendritic spine remodeling and the RyR2 upregulation induced by BDNF, and (ii) that RyR2 channel expression is crucial for spatial memory processes.

Palabras clave

Palabras clave de autor:BDNF; reactive oxygen species; Ca2+ signals; dendritic spines; NADPH oxidase; spatial memory training

KeyWords Plus:LONG-TERM POTENTIATION; NITRIC-OXIDE SYNTHASE; D-ASPARTATE RECEPTOR; ACTIVITY-DEPENDENT RELEASE; DENDRITIC SPINE GEOMETRY; NEUROTROPHIC FACTOR; SYNAPTIC PLASTICITY; RYANODINE RECEPTORS; HYDROGEN-PEROXIDE; CA2+ RELEASE

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