1. Record Nr. TD21001684

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Titolo	A MECHANISTIC APPROACH TO SYNAPTIC PLASTICITY AND COGNITION:SYNAPTIC STABILIZATION OF NMDARS THROUGH THE NOVEL INTERACTOR RABPHILIN-3A [Tesi di dottorato]
Editore	Università degli Studi di Milano, 2021-01-13
Lingua di pubblicazione	Inglese
Formato	Tesi di dottorato
Livello bibliografico	Monografia
Note	diritti: info:eu-repo/semantics/openAccess In relazione con info:eu-repo/semantics/altIdentifier/hdl/2434/793509
Sommario	The glutamatergic synapse is involved in the modulation of higher brain functions, such as learning and memory processes. The activation of specific subtypes of N-methyl-D-aspartate-type glutamate receptors (NMDARs) located at synapses accounts for different electrophysiological properties of neurotransmission and consequent synaptic plasticity mechanisms. NMDAR subunit composition is relevant for physiological neuronal functions and is often altered in many neurological disorders. In particular, augmented levels of synaptic NMDARs containing the GluN2A subunit can be observed after potentiation of neurotransmission during Long-Term Potentiation (LTP). Several studies revealed that LTP at hippocampal synapses underlies encoding and consolidation of memory. Rabphilin-3A (Rph3A) was recently characterized as a specific GluN2A intracellular binding partner promoting stabilization of GluN2A containing NMDARs at postsynapses through a trimeric complex with the main postsynaptic scaffolding protein PSD-95. Silencing of Rph3A or disruption of Rph3A/GluN2A/PSD-95 interactions leads to reduction in GluN2A-containing NMDARs due to receptor endocytosis. The modulation of this complex in the striatum of parkinsonian animals showing a dyskinetic behavior was able to

	restore normal locomotive behavior, indicating Rph3A could represent a new pharmacological target in brain diseases. However, the role of Rph3A in hippocampal functions such as synaptic plasticity and learning and memory has not yet been elucidated. In the present PhD project we aimed to investigate the role of Rph3A/GluN2A/PSD-95 complex in these events applying different stimulation protocols both in vitro and in vivo. In addition, we investigated the possible interplay between these synaptic complexes and the synapse-to-nucleus messenger Ring Finger Protein 10 (RNF10). We discovered that Rph3A is present in almost 50% of hippocampal dendritic spines at resting conditions. However, after potentiation of neurotransmission the number of Rph3A positive spines increases, paralleled by augmented formation of Rph3A/GluN2A/PSD-95 trimeric complex. Interference with Rph3A/GluN2A interaction through different experimental approaches leads to failure in LTP induction both at molecular and morphological levels, impairing also hippocampal dependent spatial learning. Dendritic spines displaying Rph3A show higher maturation degree in morphological parameters and recruit more newly-synthetized proteins compared to Rph3A negative ones, suggesting that Rph3A positive spines represent more stable and mature neuronal connections. Furthermore, the molecular motor transporter Myosin-VA was previously described as a binding partner of Rph3A and involved in GluA1-containing AMPA receptors delivery to synapses during synaptic potentiation. Interestingly, a trimeric complex composed by Rph3A/MyoVA/GluA1 is detected in hippocampus and their interaction is increased after cLTP application. Finally, our results show that impairing the synapse-to-nucleus transport of RNF10 during chemical-LTP is detrimental for Rph3A synaptic localization, indicating the integration of synapse-to-nucleus signals during synaptic plasticity probably impacts on Rph3A postsynaptic functions. In conclusion, our results suggest that Rph3A postsynaptic role is not only given by the stabilization of GluN2A containing NMDARs accounting for adequate LTP induction and hippocampal learning process, but also for modulation of synaptic responsiveness through the delivery of GluA1-containing AMPA receptors during synaptic potentiation.
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