

REGULATION OF D1 RECEPTOR TRAFFICKING AND DESENSITIZATION BY OLIGOMERIZATION WITH GLUTAMATE NMDA RECEPTOR

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Striatal medium spiny neurons express both D1 and D2 dopamine receptors and ionotropic glutamate receptors. In particular, D1 receptors are localized in neuronal spines, both in the spine shaft and in the spine head and in the post synaptic density (PSD), where NMDA receptors and their scaffolding proteins are co-clustered. The overlap in the subcellular distribution of NMDA and D₁ receptors and the observation that both D₁ and NMDA trafficking to synapses is dependent on glutamate transmission suggest that direct receptor-receptor interactions might occur. In this study, by using a combination of co-immunoprecipitation, pull-out with GST-fusion proteins and bioluminescence resonance energy transfer (BRET), we report that the D₁ receptor forms a heteromeric complex with the NMDA receptor. The D₁ receptor co-immunoprecipitated with NMDA receptor subunits from purified striatal PSD, suggesting that they are co-clustered in this structure. That this clustering reflects the existence of direct protein-protein interactions was demonstrated by BRET. A significant and specific BRET signal was found when D1 fused to Renilla luciferase (D1-Rluc) and NR1 fused to green fluorescent protein (NR1-GFP) were co-transfected in COS-7 cells. This interaction was insensitive to agonist stimulation.

By using confocal microscopy we analysed HEK 293 cells transfected with D1 and NR1 either individually or simultaneously to identify the cellular compartment where D1 and NR1 are assembled. As previously reported when expressed alone NR1 was not target to the cell membrane and was accumulated in the perinuclear region and in the endoplasmic reticulum (ER). By contrast, the D1 receptor expressed in HEK293 cells was readily and completely targeted to the plasma membrane with no ER staining. When D1 and NR1 were co-expressed in the same cells, NR1 was delivered to the plasma membrane together with the D1 receptor suggesting that the two receptors are assembled as dimeric units in the ER and transported to the cell surface as a preformed complex.

Taken together these observations point to a constitutive, direct and selective interaction of D₁ with NR1.

List of most relevant papers related with the topic

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FIG. 1: in striatal neurons D1 receptors are co-localized with NMDA in the PSD and co-immunoprecipitate with the NR1 subunit of NMDA receptor from PSD preparations

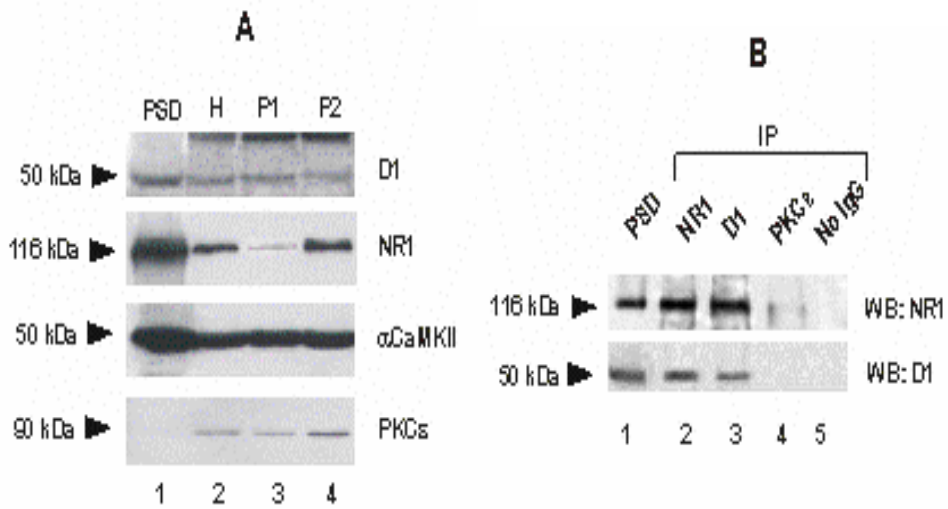


FIG 2: oligomerization with NMDA abolishes agonist-mediated D1 receptor sequestration

