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Nicotinic Acetylcholine Receptor is Internalized via a Rac-dependent, Dynamin-Independent Endocytic Pathway

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Objectives. Endocytosis of the nicotinic acetylcholine receptor (AChR) is a proposed mechanism of neuromodulation at neuromuscular junctions and in the central nervous system. Here we characterize muscle-type AChR internalization in mammalian cells.

Methods. To label AChR we used fluorescence derivatives of the competitive antagonist α-bungarotoxin (αBTX) or monoclonal antibodies against the α subunit. Cells were imaged using a combination of wide-field, confocal, and TIRF microscopies.

Results. Binding of αBTX or antibody-mediated crosslinking induces the internalization of cell-surface AChR to late endosomes when expressed heterologously in CHO cells or endogenously in C2C12 myocytes. Internalization occurs via sequestration of AChR-αBTX complexes in narrow, tubular, surface-connected compartments, as shown by differential surface-accessibility of fluorescently-tagged αBTX-AChR complexes to small and large molecules, and real-time TIRF imaging. Internalization occurs in the absence of clathrin, caveolin or dynamin, but requires actin-polymerization. αBTX-binding triggers c-Src phosphorylation, and subsequently activates the Rho GTPase Rac1. Consequently, inhibition of c-Src kinase activity, Rac1 activity or actin polymerization inhibits internalization via this unusual endocytic mechanism.

Conclusions. AChR is internalized via a novel, Rac-dependent, dynamin-independent endocytic pathway. This pathway may regulate AChR levels at ligand-gated synapses.

Palavras-Chave: AChR endocytosis bungarotoxin

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