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Dual Signaling Modes of Alpha7 Nicotinic Acetylcholine Receptors (α7 nAChRs)

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Commentary

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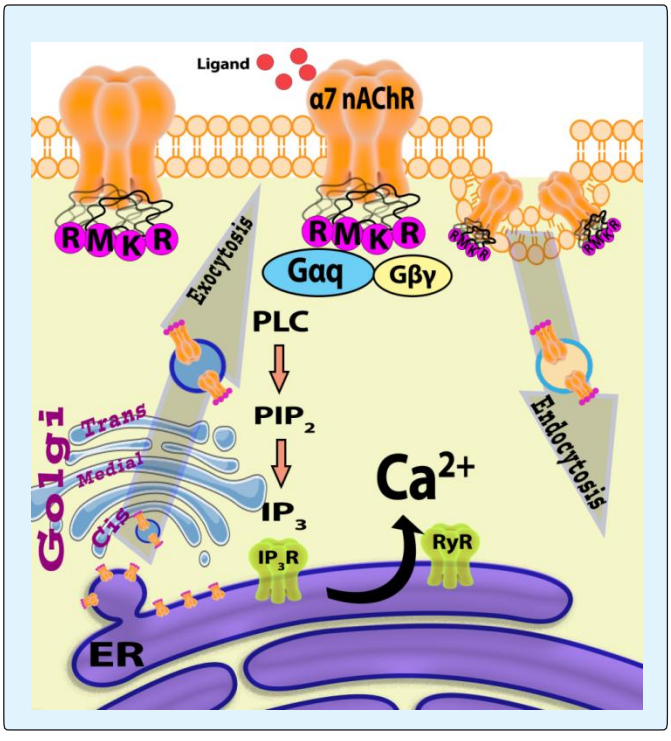
Introduction

This themed section of the Annals of Experimental and Molecular Biology is the product of an article that is focusing on metabotropic signaling of an ionotropic channel alpha7 nicotinic ACh receptors (α7 nAChRs). The article talks about how α7 nAChR, being an ion channel, can function in a metabotropic-signaling mode via G-protein coupling followed by Gαq-PLC-IP3-Ca2+ release [1]. This increases prolonged intracellular calcium signaling that would change the downstream cellular functions. The exact time-to-time processes of how the ionotropic and metabotropic signaling occurs in α7 nAChRs is an important question which will, in turn, lead to new drug development as α7 nAChRs as involved in in several disease processes including Alzheimer's disease, Parkinson's disease, as well as in nicotine addiction.

nAChRs have been representing the prototypical example for the family of pentameric ligand-gated ion channels (LGIC) that includes GABA receptors, glycine receptors, 5-HT3 receptors and glutamate receptors [2]. α7 and α4β2 subtypes are the most abundant nAChRs in the hippocampus [3,4]. Interestingly, α7 receptors have more calcium permeability and a higher desensitization rate than α4β2 nAChRs [4]. With the help of advanced mass spectrometry technologies to generate interactomes, Kabbani, et al. has shown that the cys-loop receptor, α7 nAChR, contains a conserved G protein-binding cluster (GPBC) in the transmembrane M3-M4 loop Figure 1 [1,5]. It has been shown that α7 nAChRs functionally articulate G proteins in pheochromocytoma line12 (PC12) cells [1]. When the α7345A-348A mutant was expressed, the interaction between G proteins and α7 nAChRs in PC12 cells was inhibited. Various LGICs (such as Kainate receptors, AMPA receptors, NMDA receptors, Delta receptors) are reported to function in dual manner i.e., as classical ionotropic channels and as non-canonical metabotropic signaling receptors [6,7]. Recently, King, et al. further reported that G protein coupling is crucial for α7 nAChR-mediated stimulation of RhoA and the modulation of cytoskeletal growth in PC12 cells [8]. This suggests the RhoA guanine exchange factors (GEFs) participate in G protein stimulation during metabotropic signaling of α7 nAChRs. Even if α7 nAChRs are mostly expressed in homopentameric receptors, recently heteromeric α7β2 nAChRs have been found in some brain regions [9].



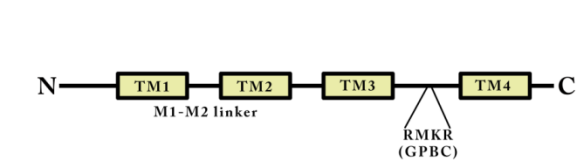


Figure 1: (A) After ligand activation of homopentameric α7 nAChRs calcium ion conductance across the plasma membrane occurs and the activation of G protein and downstream PLC signaling causes increased intracellular calcium release. (B) Schematic of the α7 subunit depicting the transmembrane (TM) domains and the intracellular M3–M4 loop which contains the sequence RMKR i.e., G protein-binding cluster (GPBC).

The correlation and significance between the ionotropic and metabotropic mechanisms for LGICs remain unclear. This type of dual mechanism for LGICs, especially α7 nAChRs, also raises important questions for example, what is the interplay of ionotropic and metabotropic α7 nAChR activities after and/or before the ligand binding? How much single channel properties of α7 nAChRs affect the overall ionotropic and metabotropic signaling? Does metabotropic signaling sustain after the receptor is in an inactivated state? Is the metabotropic signaling active even at the time when the receptor is in vesicles (while trafficking and endocytosis) and not yet expressed on the membrane? The big challenge is to make a distinction between α7 nAChR ionotropic and metabotropic activities spatiotemporally. Can the other α subunits of nAChR function with the dual mechanism? Almost all of the experiments that show α7/G protein coupled signaling are in vitro studies. It will be challenging to design experiments and test the same hypothesis in vivo to see how the dual signaling for α7 nAChR is distinctively observed in real time. As α7 nAChR is one of the prime targets for several neurological diseases, it is very important to address these questions to open new horizons for the drug discovery in the neurology.

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