ROLE OF RARE MISSENSE VARIANTS OF THE HUMAN β4 (BETA) SUBUNIT IN THE EXPRESSION AND SURFACE EXPOSURE OF α3β4 NICOTINIC RECEPTORS

Neuronal nicotinic acetylcholine receptors (nAChRs) are a family of cationic channels consisting of nine α (α2-α10) and three β subunits (β2-β4) which assemble in pentamers with different subunit composition. Two ligand binding sites are present at the interface between α and β pairs while the subunit in fifth position, that doesn’t participate in the ligand binding, is called “accessory subunit”. This subunit could be α or β leading to the formation of pentamers with two alternative stoichiometries: 2α/3β and 3α/2β that have similar agonist sensitivity but different antagonist sensitivity, and markedly different single-channel conductance.

To investigate the role of the subunit present in fifth position in the α3β4 nAChRs we set up a system to express single population of pentameric receptors with fixed stoichiometry. We found that the type of accessory subunit present in the fifth position in the pentamers determines the trafficking of the receptor to the cell surface. This study demonstrates a novel function of the accessory subunit in the α3β4 receptor that may be relevant also for other pentameric receptors (Crespi et al., 2018).

Recently, some rare missense variants of the human β4 nicotinic receptor subunit have been identified and the role of these single nucleotide polymorphisms (SNPs) in CHRNβ4 (the gene coding for the β4 nicotinic receptor subunit) have been linked to altered risk of nicotine dependence (Slimak et al, 2014). Habenular expression of these β4 variants in mice revealed a critical role of these subunits in nicotine consumption and their co-expression with the α3 subunit in hippocampal neurons, significantly altered the amplitude of nicotine-evoked currents. Taking advantage of the system that we have developed, we investigated the role of the β4 variants present in fifth position in the expression and exposure to the surface of α3β4 nAChRs.


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