A conserved arginine with non-conserved function is a key determinant of agonist selectivity in αβββ7 nicotinic acetylcholine receptors

Teresa Minguez[1], Beatriz Neilsen[2], Deborah Shoemark[3], Cecilia Gotti[4], Richard Sessions[3], Adrian Mulholland[3], Cecilia Bouzat[5], Susan Wonnacott[6], Tim Gallagher[3], Isabel Bermudez[1], and Ana Oliveira[3]

[1]Oxford Brookes University
[2]Universidad Nacional del Sur Departamento de Biología Bioquímica y Farmacia
[3]University of Bristol
[4]Consiglio Nazionale delle Ricerche
[5]INIBIBB CONICET/UNS
[6]University of Bath

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Abstract

BACKGROUND AND PURPOSE: The α7 and α4β2* (* denotes possibly assembly with another subunit) nicotinic acetylcholine receptors (nAChR) are the most abundant nAChR in the mammalian brain. These subtypes are also the most commonly targeted nAChR in drug discovery programs for brain disorders. However, the development of subtype-specific agonists remains challenging, mainly due to the high degree of sequence homology coupled to the conservation of function in the nAChR family. Here, we determined the structural underpinning of the selectivity of 10-methylcytisine, a compound with high-affinity for α4β2* nAChR but negligible selectivity for the α7 subtype. **EXPERIMENTAL APPROACH:** The structural underpinning of the receptor selectivity of 10-methylcytisine was investigated using molecular dynamics simulations combined with mutagenesis and whole-cell and single-channel current recordings. **KEY RESULTS:** We identify a conserved arginine residue in the β3-strand that exhibits a non-conserved salt-bridge in the nAChR family. In α4β2 nAChR, the arginine forms an inter-subunit salt-bridge with an aspartate residue in loop B that is necessary for functional expression, whereas in the α7 subtype, this residue is not stabilised by electrostatic interactions, making its side chain highly mobile. This produces steric clashes with agonists and affects the dynamics of residues involved in agonist binding or the coupling network. **CONCLUSIONS AND IMPLICATIONS:** We conclude that the high mobility of the arginine residue in the α7 nAChR subtype affects agonist function by influencing agonist binding and the pathway communicating agonist binding to the ion channel. The findings have implications for the rational design of subtype-selective cholinergic agents.

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