Biochemical Pharmacology 78 (2009) 899–925

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Poster abstracts

Nicotinic Acetylcholine Receptors as Therapeutic Targets: Emerging Frontiers in Basic Research and Clinical Science
October 14–16, 2009, Chicago, IL

Section 1. Basic sciences

1.1

Functional consequences of adaptive evolution of the mammalian α9α10 nicotinic receptor

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The α9α10 nicotinic acetylcholine receptor (nAChR) mediates efferent inhibition of cochlear hair cells in mammals and birds. This inhibition results from activation of calcium-dependent potassium current thought to depend on calcium entry through the activated nAChR. Sequence analysis of the *CHRNA10* genes (but not of *CHRNA9*) of different species revealed signs of adaptive evolution in the mammalian lineage [1]. Therefore, one could propose that the mammalian α9α10 receptor (i.e., from the rat, *Rattus norvegicus*) would have functional properties different from those of the avian receptor (i.e., from the chicken, *Gallus gallus*) as a result of specific, adaptive non-synonymous substitutions acquired by the *CHRNA10* gene in the mammalian lineage. To begin to test this hypothesis, we analyzed the properties of the recombinant chicken α9α10 receptor, using the two-electrode voltage-clamp technique in *Xenopus laevis* oocytes expressing these subunits. The sensitivity to acetylcholine of the *G. gallus* receptor was lower than that of the *R. norvegicus* receptor (EC_{50} = 21.7 ± 1.2 μM and 13.8 ± 1.7 μM, respectively). In addition, the *G. gallus* α9α10 receptor did not desensitize significantly, in a manner similar to that of the homomeric α9 from rat, and different from the strong desensitization of the heteromeric α9α10 *R. norvegicus* receptor. Perhaps most notably, the oocyte's endogenous calcium dependent chloride current stimulated by rat α9α10 was not activated by the *G. gallus* α9α10 receptors, suggesting that calcium permeability of the avian receptor is substantially lower than that of the mammalian receptor. These results indicate that the process of adaptive evolution in the mammalian α9α10 receptor resulted in new functional properties which are different from those of the homologous receptor in non-mammalian vertebrate species.

Acknowledgement: Supported by NIH, HHMI, UBA and ANPCyT.

Reference

[1] Franchini LF, Egoyhen AB. Adaptive evolution in mammalian proteins involved in cochlear outer hair cell electromotility. Mol Phylogenet Evol 2006;41(3):622–35.

doi:10.1016/j.bcp.2009.06.030

1.2

The nicotinic acetylcholine receptors of *Ascaris suum*

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Parasitic nematodes are important aetiological agents of disease in humans and domesticated animals. Currently, and for the foreseeable future, control of these infections of is largely via treatment with chemical anthelmintics. Nicotinic acetylcholine receptors (nAChRs) are significant drug targets for human and animal parasitic nematodes, with pyrantel and levamisole being notable examples, and a new class of drugs, the amino-acetonitrile derivatives, currently in development. However, increasing anthelmintic resistance presents a problem for sustainable helminth control. Despite their importance as drug targets in parasites, most molecular studies of nematode nAChRs have previously been carried out using *C. elegans*. Using a bioinformatics approach, we found that the parasites *Brugia malayi* and *Trichinella spiralis* have fewer nAChR genes than *C. elegans*, but some subunits of the levamisole-sensitive neuromuscular nAChR (*unc-38, unc-29* and *unc-63*) are well conserved. We have cloned cDNAs encoding UNC-29 and UNC-38 from *Ascaris suum (A. suum)*; antibody labelling shows that *Ascaris* UNC-