Biochemical Pharmacology 82 (2011) 1023–1047

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 & Clinical Sciences November 9–11, 2011, Washington, DC

Section 1. *In vitro* pharmacology and basic sciences

1.1

Functional examination of human α4β2α5 nicotinic AChRs transfected in SH-EP1 cells

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Recent genetic studies suggested an involvement of the accessory α5 nicotinic acetylcholine receptor (nAChR) subunit in nicotine dependence. Using *Xenopus oocytes* expression system, it has been shown that α5 subunit can co-assemble with αβ heteromers to form functional nAChR [1,2]. Here, we report on the result of incorporation of α5 subunit in human α4β2 nAChRs permanently transfected in SH-EP1 cells. Patch-clamp technique in a whole-cell configuration was used to examine the agonist activity of ACh, nicotine and varenicline on α4β2α5 nAChRs and compare to that in the parent α4β2 nAChR cell line. Both ACh and nicotine acted as a full agonist in α4β2 nAChRs with the EC_{50} values of ~17.1 and ~3.9 μM, respectively, while varenicline activated currents with an EC_{50} of ~0.32 μM and an efficacy of 62.1% relative to the maximum ACh (1 mM)-induced response. Incorporation of the α5 subunit in α4β2 nAChRs resulted in a biphasic dose-response relationship for ACh and nicotine. The EC_{50} values for low- and high-affinity components were ~1.06 and ~53.2 μM for ACh and ~0.01 and 17.2 μM for nicotine, respectively. Similar to that in α4β2 nAChRs, varenicline behaved as a partial agonist with an EC_{50} of ~0.29 μM and an efficacy of 37.4% relative to the maximum ACh (1 mM)-induced response. Our data suggest that incorporation of α5 subunit in human α4β2 nAChRs permanently transfected in SH-EP1 cells results in formation of functional α4β2α5 nAChRs that exhibit altered sensitivity to ACh and nicotine and efficacy of varenicline.

References

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doi:10.1016/j.bcp.2011.07.003

0006-2952/$ – see front matter
doi:10.1016/j.bcp.2011.07.002

1.2

The conundrum of the α5 nicotinic acetylcholine receptor subunit

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The history of the α5 subunit of the nicotinic acetylcholine receptor began with the identification of its coding sequence showing multiple particularities that brought molecular biologists to speculate that this gene probably belonged to the serotoninergic family. Whilst this was soon corrected, the role of the α5 subunit remained speculative and functional expression yielded several interpretations ranging from a structural to complementary subunit. The heated debate around the α5 subunit rose with the identification of the association between the genotype of α5 and smoking behavior phenotype and the highest probability of some variants for developing a lung cancer. Moreover, it was recently shown that knockout of the α5 subunit in the median habenula profoundly modified the animal behavior in nicotine addiction model [1]. In this work we reexamined, in the light of the latest knowledge, the role of the human α5 subunit in recombinant receptors expressed in *Xenopus* oocytes. Expression of the human α5 subunit with α4 and β2 revealed that introduction of this subunit in receptor complexes caused significant pharmacological differences. Oocytes expressing the α5 subunit displayed larger ACh-evoked currents than sibling oocytes injected only with α4 and β2. This current increase was associated with a higher sensitivity to ACh. The expression of different ratios of α5 versus α4 and β2 allowed to examine the effects of this subunit on the high and low affinity α4β2 nAChRs. Immunoprecipitation of membrane receptors carried out in parallel with functional studies provided a further insight in receptor stoichiometry and the correlation with the pharmacological signature of these receptors. Altogether, these data further support the hypothesis that α5 plays a significant role in the central brain nAChRs functions and constitutes a novel therapeutic target.

Acknowledgments: This work was supported by the EEC grant Neurocypres to DB and CG.

Reference

[1] Fowler CD, et al. Nature 2011;471:597.

doi:10.1016/j.bcp.2011.07.004