Abstract

Nicotinic acetylcholine receptors (nAChRs) are involved in a variety of human behaviors such as addiction, attention, and memory. Proteins from the Ly-6/uPAR family also known as prototoxins have been identified as accessory modulators of signaling through nAChRs; however, the specificity of prototoxins and their functions have yet to be thoroughly explored. We previously discovered that the prototoxins LYPD6B and PSCA are expressed in the avian ciliary ganglion. Since PSCA limits ACh induced activation of α7, we hypothesized that LYPD6B would modulate α3* containing nAChR heteromers that include α3, β4 and α5 subunits (the other prominent ganglionic subtype). To test this hypothesis, we determined whether the co-expression of LYPD6B with varying α3, β4 and α5 containing nAChR concatemers in *Xenopus* oocytes causes differences in ACh sensitivity (EC50), alters the maximum current induced by ACh (Imax) and/or changes the rate of desensitization (τ) caused by ACh. LYPD6B specifically enhances the affinity of activation, reduces the Imax and desensitization rate of ACh-elicited function of (α3)3(β4)2 nAChR, while leaving unaffected the function of (α3)2(β4)3 or α7 homomorphic nAChR. For (α3)2(β4)2α5 nAChR, there is no shift in the EC50 or τ values of ACh-induced function, but there is a decrease in the Imax. Thus, the effects of LYPD6B discriminate between nAChR subtypes, and even between stoichiometries of α3β4 nAChR. These results suggest that the modulatory effects of prototoxins on nAChRs can be complex and highly specific.